Medical-Statistical Review:
NDA 20-665/SE1-016 and 21-283/SE1-001
Diovan (valsartan) Capsules and Tablets

September 13, 2001

Primary Medical Reviewers: Shari L. Targum, MD, Medical Officer, Division of Cardio-Renal Drug Products, HFD-110, ODE1/CDER.
(Study 110 was reviewed by: Abraham Karkowky, MD, PhD, Team Leader, Division of Cardio-Renal Drug Products, HFD-110, ODE1/CDER.)

Statistical Reviewer: Study 107 was reviewed by: H.M. James Hung, PhD, Statistician/Team Leader, Division of Biostatistics, HFD-710, CDER.

TABLE OF CONTENTS:

Recommendation on Approvability

Medical Reviewer's Comments:

As seen in the Val-heft study (107), no survival benefit has been demonstrated with valsartan. However, benefit was seen with valsartan with respect to prolonging the time to first morbid event, as driven by CHF hospitalization. Subgroup analysis shows greater valsartan benefit (mortality and morbidity) in the subgroups not on background ACE inhibitor or beta blocker, versus those patients on background ACE inhibitors/beta blockers (albeit with small numbers of patients not on background ACE inhibitors). The results were less favorable in the US population compared to the non-US population. Some secondary endpoints (LHFQ, EF, signs/symptoms, neurohormone measurements) have been favorable for valsartan (consistently only in Study 107). Interestingly, the increase in EF and neurohormones in this study population were not accompanied by a survival benefit. No benefit has been demonstrated for valsartan in prolonging the time to all-cause hospitalization, and the Days Alive/Out of hospital analysis did not show a substantial difference in favor of valsartan.

Outstanding questions and requests for the sponsor include: 1. Primary reason for non-CHF hospitalization; 2. Further analysis of renal safety, including numbers of patients dialyzed; 3. SAS code for first hospitalization; 4. Case report forms for angioedema.

The medical reviewer concludes that valsartan appears to have some beneficial effect in terms of CHF hospitalization. A remaining issue is whether this benefit is "offset" by safety issues related to this drug, and whether drug-related side effects contribute to the lack of significant benefit seen in "all-cause" hospitalization. The Agency, at the time of this review, is still awaiting further data/analysis from the sponsor regarding this issue.

If convincing information can be presented to alleviate this concern, then the Medical Reviewer would recommend that valsartan is approvable in prolonging the time to first morbid event in this particular patient population. (The reviewer wonders if the outcome would have been different if, for example, there had been a higher usage of beta blockers in this patient population).

Recommendation on Phase 4 Studies and/or Risk Management Steps

Further studies of Valsartan in CHF could include:

- The role of valsartan in treatment of CHF in those patients who are intolerant to ACE inhibitors. Ideally, this type of trial would be placebo-controlled, evaluating morbid/mortal outcomes.

Since the numbers of Black patients was relatively small compared to the total, this reviewer would be interested in:

- The efficacy and safety of valsartan in CHF therapy in the Black population.

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Valsartan (Diovan) is an orally active competitive angiotensin II antagonist approved for the treatment of hypertension. The recommended starting dose is 80 mg once daily in patients who are not volume-depleted. Valsartan may be used over a dose range of 80 to 320 mg once daily. No initial dosage adjustment is required for the elderly or those with mild to moderate hepatic or renal insufficiency. Safety and efficacy in pediatric patients has not been established.

The Sponsor has submitted an efficacy supplement for the treatment of CHF. The proposed regimen is a starting dose of 40 mg twice daily, with uptitration to 80 mg and 160 mg twice daily to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 160 mg twice daily.

B. State of Armamentarium for Indication(s)

There are currently no angiotensin-II antagonists approved for the treatment of CHF.

Current therapy for CHF includes the use of: diuretics, digitalis, ACE inhibitors, beta blockers (such as carvedilol and metoprolol (symptomatic Class II and III CHF).

C. Important Milestones in Product Development

1. In a July 7, 1994 telephone conference with the Agency, the Vheft-IV study, a 3-4 year, randomized, double-blind, placebo-controlled, forced titration study in about 600-1,000 NYHA Class II-IV patients, was discussed. This was planned as one trial in patients on a background of ACE inhibitors, diuretics and digoxin and another trial in patients who are intolerant to ACE inhibitors, on a background of digoxin and diuretics. The arm with ACE inhibitor-intolerant patients was planned with exercise tolerance as an endpoint, since it was felt that the sample size would be insufficient for a mortality endpoint. The Agency responded that unless the results were quite significant for a survival benefit (i.e., p of less than 0.0025), the Agency would have to "think a long time" about what to do with the supplement. The Agency encouraged the sponsor to conduct dose-ranging morbidity/mortality trials. In addition, the Agency expressed discomfort if Vheft-IV were the only source of data, but would likely accept Vheft-IV plus two or more ETT trials; however, the Agency needed to know the trial designs in greater detail.
2. In an April 5, 1996 End-of-Phase II meeting, it was noted that choosing an appropriate endpoint in CHF trials was difficult. For a combined endpoint, there may be approvability issues if all parts of the combined endpoint do not have results in the same direction. Furthermore, approval based on one trial would need robust results, dose-related effects, or other reasons to believe that results were reproducible. The sponsor agreed to revise the stopping rule for Study 107 (to be based on mortality alone). The sponsor also considered having two primary endpoints, all-cause mortality and the combined endpoint (for 107). The sponsor planned to send a sealed copy of the randomization codes to their IND, and provide pharmacokinetic data from CHF patients given BID dosing.

D. Other Relevant Information

Valsartan is currently marketed in many countries for the indication of hypertension. At the time of the submission, an application was being made to the German health authority for the treatment of heart failure.

E. Important Issues with Pharmacologically Related Agents

Since approval of angiotensin-II antagonists (sartans) for the treatment of hypertension, there have been reports of elevated liver function tests.
In addition, there have been rare reports of angioedema and anaphylactic reactions.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

According to the assigned chemist, a pending issue in this submission involves expiration dates for this drug. For further detailed information, please see the review by the assigned chemist.
An abbreviated preclinical pharmacology summary was submitted (Volume 1). There was evidence, based on animal models, that valsartan reduced preload (dog model) and reduced systemic and pulmonary vascular resistance without affecting arterial blood pressure (pig model). In another dog study, long-term valsartan therapy decreased preload and afterload in moderate heart failure but provided only limited benefit in attenuating progression of LV dysfunction. Some favorable outcomes were noted regarding remodeling.
No animal pharmacology/toxicology issues have been identified with this submission.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics/Pharmacodynamics

The pharmacokinetics of valsartan in CHF patients are similar to those of healthy volunteers with respect to linearity, Tmax (about 3 hours), T1/2 (about 6.5 hours) and age effects. Valsartan clearance was about 10-20% lower in the elderly CHF patients compared to younger CHF patients.
The clearance of valsartan appears to be reduced about 50% in patients with CHF compared to healthy subjects. Cmax and AUC are ~1.3 to 2 times higher in patients with CHF compared to healthy subjects. Accumulation of valsartan is slightly greated in patients with CHF when dosed at 40-160 mg BID compared to once daily in hypertensives.
For further detailed discussion, please see the Clinical Pharmacology and Biopharmaceutics Review.

IV. Description of Clinical Data and Sources

A. Overall Data

The source of data used in the review consisted of the clinical trials conducted by the sponsor (see Table 1). In addition, there was an uncontrolled study (ANG 102) report in the efficacy supplement which was unaccompanied by a database.

In addition, literature reports, current labeling and postmarketing data were used as needed.

Integrated Summary of Efficacy:
The five double-blind studies are summarized in Table 1 (below).

Table 1. Double-blind Studies

Study	Control	Treatment duration	No. randomized	CHF Class	Entry criteria	Treatment	Efficacy
103	Placebo/active	4 weeks	116	II-IV	PCWP≥15 mmHg (-ACE)	V40 bid, V 80 bid, V 160 bid, PBO, Lis 5/10 qd	Hemodynamics and neurohormones
104	Placebo	4 weeks	83	II-IV	LVEF ≤ 40%, PCWP >15 mmHg (+ACE)	V 80 bid, V 160 bid, PBO	Hemodynamics and neurohormones
106	Placebo	16 weeks	770	II-IV	LVEF ≤ 40% (+/-ACE)	V 40 bid, V 80 bid, V 160 bid, PBO	ETT, LHFQ, signs/symptoms, NYHA, EF
107	Placebo	24-36 months	5010	II-IV	LVEF < 40, LVIDD>2.9mm /m^2, (+/-ACE)	V 40-160 bid forced titration, PBO	Morbid/mortal, 6 min. walk substudy, signs/symptoms, NYHA, LHFQ, EF, LVIDD, neurohormones
110	Active	12 weeks	141	II-III	LVEF ≤ 45% +prior ACE	V 80-160 bid, Enal 5/10 bid, titration	6 min. walk, signs/symptoms, NYHA, LHFQ, AVPD, LVIDD

Study 102. This was a 3-site open-label, placebo-controlled, single-dose study of the effects of valsartan 10, 20, 40, 80 and 160 mg and placebo on central hemodynamic and neurohormone measurements in patients with Class III-IV stable CHF. Three to five patients were randomized per treatment group. The primary efficacy parameter was the change from baseline in PCWP and CO at 1, 2, 3, 4, 6, 8 and 12 hours after dosing. Baseline imbalances were seen between placebo and treatment groups (PCWP higher in placebo and showed largest decreases). No dose-response pattern could be seen in reviewing the hemodynamic data. Valsartan exhibited linear kinetics consistent with that seen in healthy volunteers. There was a trend toward increase in placebo-adjusted mean change for PRA and Ang II and a decrease in aldosterone concentrations with increasing valsartan concentrations.

Study 103. This was a 9-site double-blind, randomized, placebo and active-controlled study of the effects of valsartan 40, 80, and 160 BID, placebo, and lisinopril 5 titrated to 10 mg QD on central hemodynamic and neurohormone measurements in patients with stable Class III-IV CHF. Patients were allowed in this trial if they were not taking ACE inhibitors for 6 months prior to Visit 1. The primary efficacy variable was the change from baseline in PCWP. Twenty-four to 27 patients were randomized to valsartan or placebo, and 15 patients were randomized to lisinopril. At Day 28, valsartan 40 BID and 160 BID showed a statistically significant decrease in PCWP compared to placebo; the results for valsartan 80 BID were inconsistent and showed a nonsignificant trend at 12 hours post-dosing. Study 103 will not be used by the medical reviewer for decision-making; please see the detailed study review for further details.

Study 104. This was a multicenter, double-blind, randomized, placebo-controlled 4 week study of Class II-IV CHF patients on background ACE therapy. Eighty-three patients were randomized to either valsartan 80 BID, valsartan 160 Bid or placebo. The primary efficacy parameter was the change from baseline in PCWP. Other measures included other hemodynamic parameters and neurohormones.

Study 106. This was a multicenter, double-blind, randomized, placebo-controlled study evaluating effects of valsartan 40 BID, 80 BID, 160 BID or placebo on exercise time and the LHFQ. Seven hundred seventy patients were randomized. The primary efficacy parameters were change in mean exercise tolerance time (ETT) via modified Naughton protocol as well as the overall LHFQ. Secondary measures included signs/symptoms of CHF and EF. Patients were stratified according to ACE inhibitor use (y/n).

Study 107. This was a multinational, double-blind, forced titration, placebo-controlled study of 5010 Class II-IV CHF patients. The study was event-driven, ending after a prespecified number of deaths. Patients were randomized to valsartan 40 BID or placebo with forced titration to a maximum dose of 160 BID.
The primary efficacy parameters were: time to death and time to first morbid event (composite). Secondary variables included: time to first nonfatal morbid event, time to CHF hospitalization, time to CV death, NYHA class, signs/symptoms of CHF, change in EF, change in LVIDD, change in overall, physical and emotion LHFQ. Patients were stratified according to beta blocker use (y/n).

Study 110. This was a randomized, double-blind, active controlled 12 week study of Class II-III CHF patients on background ACE inhibitor. One hundred forty-one patients were randomized to valsartan (80 to 160 mg once daily) or enalapril (5 to 10 BID). The primary efficacy parameter was the six minute walk test.

Morbidity and mortality results:
One study, 107, evaluated the effect of valsartan on mortality and morbidity. To avoid redundancy in data presentation, the reader is referred to the Individual Study Review, where the efficacy tables are presented and the study is discussed in detail. It can be seen (Efficacy tables, Study 107) that there is no survival benefit for valsartan in this study population. However, valsartan did significantly prolong the time to first morbid event. This co-primary endpoint appears to be driven by CHF hospitalizations. Indeed, valsartan also significantly prolonged the time to first CHF hospitalization. This finding is consistent whether assessed by the Investigator or the Endpoint Adjudication Committee.
The most common cause of death in the 107 study population was sudden cardiac death. Subgroup analysis for mortality and morbidity results did not show meaningful differences in age and gender. Analysis of the mortality subgroups showed statistically significant findings only in

the group not on ACE inhibitor and the group taking beta blocker. The "no ACE" group showed a hazard ratio of 0.669 in favor of valsartan; the group on beta blocker showed as hazard ratio of 1.357 against valsartan.
Morbidity subgroups showed similar hazard ratios except that valsartan appeared to show less benefit in the US, in patients with ischemic CHF, in the subgroup with higher EF, and in Black patients (although the number of Black patients was small relative to the total). Valsartan appeared to show less benefit in the subgroup on background ACE inhibitor; the results of morbid events for patients on beta blocker appeared to be unfavorable in the valsartan group.
Further analyses of CHF hospitalization can be found in the Study Review of 107.

Exercise testing results:
Studies 106, 110 and 107 (substudy 02) utilized various exercise testing. Study 106 used a modified Naughton protocol. Studies 107 (02) and 110 used the 6 minute walk.
In all three studies there was an improvement in exercise capacity compared to baseline; this included an improvement in the placebo group. No statistically significant improvement in valsartan was seen compared to placebo. The results do not support a claim for improvement in exercise capacity for valsartan compared to placebo.

Ejection fraction results:
In both Studies 106 and 107, significant increases in LV EF were seen with valsartan compared to placebo. In study 106, significant increases were seen at endpoint for valsartan 40 mg BID and 160 mg BID (the results for 80 BID showed a nonsignificant trend).

LHFQ:
The Minnesota Living with Heart Failure Questionnaire (LHFQ) was measured in Studies 106, 107, and 110.
Only Study 107 showed statistically significant results in overall LHFQ. Subgroup analysis of the LHFQ endpoint results (107) show improvement in the "no ACE" subgroup compared to placebo (worsening). A review of the 107 emotional and physical scores also show significant improvements in the valsartan group.

Central hemodynamic measurements:
Studies 102, 103 and 104 used right heart catheterization to measure central pressures. In all three studies the primary efficacy variable involved change in PCWP.
Study 104 showed a statistically significant decrease in PCWP at peak (4-8 hours post dosing) and over 0-12 hours for valsartan 160 mg BID, the highest dose used, as measured on Day 0 (first dose). However, a statistically significant difference compared to placebo was not seen on Day 28. Statistically significant differences were seen in the decrease in PCWP compared to placebo for valsartan 160 mg BID in Study 103 (where patients were off ACE inhibitors). Because of baseline differences across treatment groups in Studies 102 and 104, the medical reviewer is cautious in the interpretation of these results.

Dyspnea-fatigue Index:
This result, from study 110, showed a slight improvement in symptoms with no statistically signficant differences.

LVIDD:
Significant decreases in LVIDD/BSA were seen in valsartan vs. placebo (107).

Neurohormone results:

Neurohormones were measured in Studies 102, 103, 104 and 107.
No conclusions can be drawn from the neurohormone results in study 102.

Study 103 only showed significant differences for angiotensin II, measured at 12 hours (trough) in the valsartan 80 mg BID group.

In study 104, baseline differences could be seen for plasma norepinephrine and atrial peptide activity. Significant decreases were seen for plasma aldosterone, compared to placebo, in valsartan treatment groups at peak, and in the valsartan 160 mg BID group at trough.

Significant decreases, compared to placebo, are seen in 107 for plasma norepinephrine and BNP.

Summary:
The major positive results can be found in Study 107. In that trial, the time to morbid event was significantly prolonged in the valsartan treatment group; this primary endpoint appears to be driven by CHF hospitalizations. A detailed discussion can be found in the Study 107 review. Findings consistent with a treatment effect include: increase in EF (Study 106 and 107), improvement in signs/symptoms of CHF (107 only), decrease in plasma norepinephrine and BNP (Study 107), decrease in LVIDD (107), and improvement in LHFQ (107). One would have hoped for more robust findings in the other studies; it may be that the studies other than 107 were "underpowered" to detect these significant differences.
Interestingly, as seen in 107, the increase in ejection fraction does not seem to accompany survival benefit in this study population.

The subgroup results for morbidity and mortality are consistent with the theory that valsartan has a more favorable effect in the absence of ACE/beta blockers. Valsartan has less of a favorable effect (morbidity) in the US compared to nonUS; the exact reason for this is unclear (the use of ACE and beta blockers in the US and nonUS populations were not analyzed).

Integrated Summary of Safety:
NDA: 20-665
S-016

Sponsor: Novartis

1.0 Materials Utilized in Review:

In evaluating the safety of valsartan, the Medical Reviewer used the electronic archive, including the SAS database, supplied by the Sponsor with the submission of NDA 20-665, S-016. The safety database analyzed in this review represented data from all completed studies up until October 1st, 2000; information from the Safety Update will not be presented in this report, but will be filed, if needed, as an addendum.

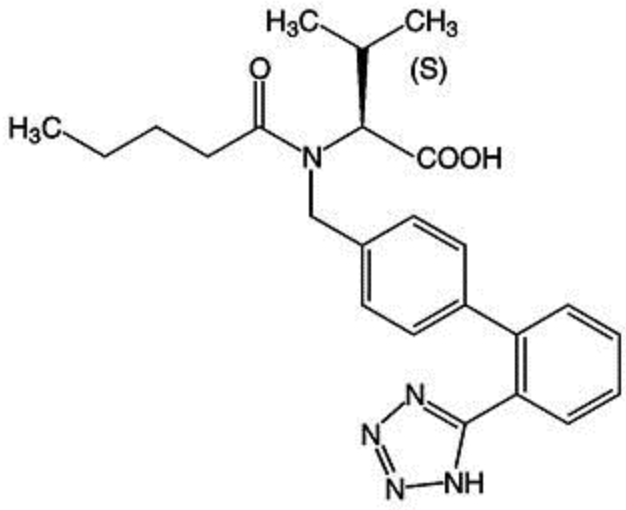
The approach used to characterize the safety profile of valsartan consisted of examination of the entire database for deaths, discontinuations, serious adverse events, as well as routine safety data (treatment emergent adverse events, laboratory tests, vital signs and ECG data).

2.0 Background-Pharmacologic Class

Valsartan is a orally active specific competitive angiotensin (Ang) II antagonist of the AT_1 subtype. Valsartan is currently approved for the treatment of hypertension in daily doses up to 320 mg.

3.0 Chemistry

Valsartan is described chemically as *N* -(1-oxopentyl)- *N* -[[2'-(1 *H* -tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-L-valine. Its empirical formula is $C_{24}H_{29}N_5O_3$, its molecular weight is 435.5, and its structural formula is :



Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water. The reader is referred to the Chemistry review for further detailed discussion.

4.0 Indication

In this NDA submission, the Sponsor is seeking an indication for valsartan for the treatment of congestive heart failure.

5.0 Post-Marketing Experience

Valsartan is approved for the treatment of hypertension in the US and is currently marketed in about 60 countries. To the best of this reviewer's knowledge, valsartan has not been withdrawn from any market.

6.0 Use in Pediatric Population

Valsartan has not been studied in population less than 18 years of age.

7.0 Animal Pharmacology/Toxicology

There is no new relevant animal safety/ toxicology data for review.

8.0 Description of Clinical Data Sources

8.1 Primary Source Data

Four safety datasets were submitted by the sponsor: A. Pooled data from 103, 104, 106, 107 (first 7 Visits) and active-controlled study 110 (primary dataset); B. Pooled data as in #1 without 110; C. Study 107 (long-term, double-blind, placebo –controlled); D. Open-label trials: 102, 105 and ANG 102.

- **Clinical Pharmacology**: This submission contained 2 small open-label clinical pharmacology studies (102, N=25, 105, N=18). Study 102 was jointly reviewed by the medical and clinical pharmacology and biopharmaceutics reviewer. Study 105 was reviewed by the clinical pharmacogy and biopharmaceutics reviewer.
- **Phase 2/3 Clinical Efficacy/Safety Studies** consisted of 5 randomized double-blind trials. This program included one large study with morbid/mortal outcomes (107), one 770 patient short-term trial (106) and three smaller short-term studies (103, 104, and 110).
- **8.1.1.Exclusions from Database**:

This database does not contain information from the 4-month Safety Update. Pertinent information will be filed, as needed, as an addendum to this review.

This safety review will focus mainly on the primary database (A, above) and Study 107 (C, above).

8.2 Safety Populations studied and their characteristics

8.2.1 Demographics

Demographic data for the Phase 2/3 trials are presented below. The primary safety dataset was a mostly male, mostly Caucasian population. Almost half were over 65, with a higher percentage of elderly and > 75 in the ACE comparator group. The active control group (ACE comparator) was 100% Caucasian. Most patients were classified as NYHA Class II and III.

Table 3. Baseline characteristics

	Valsartan					ACEI comparator	Placebo
	0 mg N=473 n (%)	80 mg N=2787 n (%)	160 mg N=2843 n (%)	320 mg N=2304 n (%)	Total N=3289 n (%)	N=86 n (%)	N=2745 n %)
Male	366 (77)	2217 (80)	2269 (80)	1840 (80)	2639 (80)	66 (77)	2205 (80)
Female	107 (21)	570 (21)	574 (20)	464 (20)	650 (20)	20 (23)	540 (20)
Mean age (yrs)	64	63	63	63	63	66	63
Age < 65 yrs	234 (49.5)	1506 (54)	1523 (54)	1245 (54)	1773 (54)	35 (41)	1431 (52)
Age ≥ 65 yrs	239 (50.5)	1281 (46)	1320 (46)	1059 (46)	1516 (46)	51 (59)	1314 (48)
Age ≥ 75 yrs	79 (17)	366 (13)	386 (14)	294 (13)	451 (14)	19 (22)	416 (15)
Race: Caucasian	416 (88)	2502 (90)	2522 (89)	2028 (88)	2918 (89)	86 (100)	2475 (90)
Black	38 (8)	204 (7)	234 (8)	199 (9)	271 (8)	0	190 (7)
Oriental/other	19 (4)	81 (3)	87 (3)	77 (3)	100 (3)	0	80 (3)
NYHA : Class I	1 (0.2)	2 (0.1)	4 (0.1)	3 (0.1)	4 (0.1)	0	5 (0.2)
II	252 (53)	1724 (62)	1761 (62)	1466 (64)	2006 (61)	56 (65)	1660 (61)
III	206 (44)	1015 (36)	1037 (37)	804 (35)	1221 (37)	27 (31)	1021 (37)
IV	14 (3)	46 (2)	41 (1)	31 (1)	58 (2)	3 (4)	59 (2)
Mean Sitting DBP (mm Hg)	73	75	75	76	75	77	76
Mean Sitting SBP (mm Hg)	120	124	124	125	123	126	124

Source: Volume 77: Table 2.2-1, 2.2-4, 2.2-7, 3.1-1, 3.1-4: Studies 103, 104, 106, 107 (first 4 months) and 110. ACEI comparator group combines lisinopril and enalapril from the active controls. Valsartan 0 mg group contains treatment interruptions from Study 107. Because of dose titrations, patients may be counted in more than one valsartan dose group, but only once in the Total column.

In terms of the primary safety database (103, 104, 106, 107 through Visit 7, and 110), mean weights were about 79-82 (±16) kg, Mean LVEF was 26-27% and mean duration of CHF was about 50-52 months. CHF etiology was about 55-57% ischemic heart disease, about 28-37% idiopathic cardiomyopathy (37% in the active control group, and about 28-31% in valsartan and

placebo), 4-8% hypertension, and 5-7% other. Results for standing diastolic and systolic blood pressures were similar to sitting BP values.

Table 4. Summary of baseline background cardiovascular therapy (primary dataset)

	Valsartan					ACEI comparator	Placebo
	0 mg N=473 n (%)	80 mg N=2787 n (%)	160 mg N=2843 n (%)	320 mg N=2304 n (%)	Total N=3289 n (%)	N=86 n (%)	N=2745 n (%)
ACE inhibitors	433 (92)	2493 (90)	2524 (89)	2097 (91)	2887 (88)	2 (2)	2511 (92)
Diuretics	426 (90)	2385 (86)	2422 (86)	1957 (85)	2807 (85)	69 (80)	2326 (85)
Digoxin	349 (74)	1846 (66)	1887 (66)	1543 (67)	2195 (67)	38 (44)	1853 (68)
Nitrates (short and long-acting)	209 (44)	1046 (38)	1048 (37)	847 (37)	1174 (36)	25 (29)	1015 (37)
Beta blockers	151 (32)	975 (35)	959 (34)	760 (33)	1074 (33)	55 (64)	930 (34)
Amiodarone	62 (13)	341 (12)	360 (13)	294 (13)	401 (12)	5 (6)	359 (13)
Calcium channel blockers	59 (13)	305 (11)	313 (11)	259 (11)	347 (11)	1 (1)	337 (12)

Source: Volume 77: Table 3-3. Includes 103, 104, 106, 107 (first 4 months) and 110. Valsartan patients are counted only once in the total column. In study 107, valsartan treatment interruptions were captured in the 0 mg column and included in the total column.

8.2.2. Extent of Exposure to valsartan

The two tables to follow list duration of exposure by dose in the Phase 2/3 Clinical Trials. Most of the exposure to valsartan appears to be in total daily doses up to 320 mg.

Table 5. Minimum exposure (days) by total daily dose—short-term

	Valsartan (total daily dose)					Active control*	Placebo
	0 mg	80 mg	160 mg	320 mg	Total		
# Days							
≥1	473	2787	2840	2302	3285	86	2743
≥30	121	534	614	2047	3041	83	2649
≥60	60	355	477	1953	2886	63	2536
≥90	18	288	296	1346	2727	6	2478

Source: Sponsor: Volume 77: Table 2.1-1: Data from 103, 104, 106, 107 (through Visit 7), 110. Patients may be counted in more than one valsartan dose group, but only once in the total column. In 107, patients with valsartan treatment interruptions during double-blind are counted in the '0 mg' column but excluded from the Total Valsartan column.
*Combines enalapril and lisinopril treatment groups.

Table 6. Minimum exposure (days) by total daily dose— (107)

	Valsartan (total daily dose)					Placebo
	0 mg	80 mg	160 mg	320 mg	Total	
# Days						
≥1	1191	2508	2342	2118	2508	2497
≥30	540	461	525	1944	2409	2428
≥60	361	310	396	1900	2323	2371
≥90	228	276	344	1848	2268	2330
≥ 180	67	224	268	1693	2155	2235
≥ 360	9	162	199	1543	1968	2063
≥ 720	0	69	77	722	1061	1108

Source: Volume 77: Table 2.1-3. . Patients may be counted in more than one valsartan dose group, but only once in the total column. Patients with valsartan treatment interruptions during double-blind are counted in the '0 mg' column but excluded from the Total Valsartan column.

Table 7. Summary of exposure (days) by total daily dose (short-term)

	Valsartan (total daily dose)					Active control	Placebo
	0 mg	80 mg	160 mg	320 mg	Total		
N	473	2787	2843	2304	3285	86	2743
Mean (SD)	24 (30)	29 (31)	30 (32)	81 (27)	107 (32)	74 (20)	114 (26)
Range	1-188	1-188	0-154	0-203	1-232	6-92	1-253

Source: Volume 77: Table 2.1-4. Includes 103, 104, 106, 107 (first 4 months) and 110. Active control combines lisinopril and enalapril. Patients may be counted in more than one dose group, but only once in the total. In 107, treatment interruptions were captured in the 0 mg group and excluded from the total column.

Table 8. Summary of exposure (days) by total daily dose (107)

	Valsartan (total daily dose)					Placebo
	0 mg	80 mg	160 mg	320 mg	Total	
N	1191	2508	2345	2120	2508	2497
Mean (SD)	52 (72)	69 (171)	84 (190)	540 (306)	604 (300)	629 (281)
Range	1-629	1-1105	0-1074	0-1113	1-1203	1-1138

Source: Volume 77: Table 2.1-6
Patients may be counted in more than one dose group, but only once in the total. Treatment interruptions were captured in the 0 mg group and excluded from the total column.

In analyzing mean duration of exposure by subgroup (age, gender, race) no meaningful differences were seen in the short-term studies (primary database). In Study 107, there appeared to be less mean days of exposure for the elderly (< 65 years, n=1367, mean days of exposure for valsartan=625.6; ≥ 65 years, n=1141, mean days of exposure= 577.9, ≥ 75 years, n=318, mean days of exposure =540.6).

Table 9. Numbers randomized and in safety analyzable database: all pooled trials combined, including 103, 104, 106, 107, 110

	Valsartan (total daily dose)					Lisinopril	Enalapril	Placebo	Total
N	0 mg	80 mg	160 mg	320 mg	Total				
randomized	1191	2787	2856	2368	3289	15	71	2745	6120
Safety analyzable	1190	2785	2855	2368	3282	15	71	2740	6108

Source: Volume 77: Table 4-2

Table 10. Patient Disposition (double-blind short-term)

	Valsartan N (%)	Active control		Placebo N (%)
		Lisinopril N (%)	Enalapril (n (%)	
Randomized	778 (100)	15 (100)	71 (100)	246 (100)
Completed	658 (85)	14 (93)	62 (87)	220 (89)
Premature discontinuation during double-blind	120 (15)	1 (7)	9 (13)	26 (11)
Adverse Event	67 (9)	0	3 (4)	9 (4)
Abnormal lab	2 (0.3)	0	0	0
Unsatisfactory therapeutic effect	1 (0.1)	0	0	1 (0.4)
Did not meet protocol criteria or noncompliant	24 (3)	0	0	5 (2)
Withdrew consent	7 (0.9)	1 (7)	1 (1)	4 (2)
Lost to follow-up	5 (0.6)	0	0	1 (0.4)
Administrative problems	4 (0.5)	0	0	2 (0.8)
Death	10 (1)	0	5 (7)	4 (2)

Source: Volume 77: Table 4-1. Includes 103, 104, 106, 110

Patient disposition for Study 107 can be found in that study review.

8.3 Adequacy of Safety Database

The Safety Database appears to be adequate for the Demographic population as noted above.

9.0. Human Pharmacokinetic Considerations

The Medical Reviewer failed to identify pharmacokinetic findings useful in explaining the occurrence of adverse events observed during clinical trials of valsartan. The reader is referred to the Clinical Pharmacology and Biopharmaceutics review for the human pharmacokinetics of valsartan and detailed information on the subject.

10.0. Integrated Review of Safety

10.1. Deaths:

The following table provides a summary of deaths by treatment and study.

Table 11. Number of deaths by principal cause (double-blind short-term trials)

	Valsartan N=778 n (%)	Active control N=86 n (%)	Placebo N=246 n (%)
Total deaths	10 (1.3)	5 (5.8)	4 (1.5)
CHF	4 (0.5)	0	0
Cardiac arrest	2 (0.3)	0	0
Sudden death unexplained	2 (0.3)	2 (2.3)	2 (0.8)
CVA NOS	1 (0.1)	0	0
Intestinal infarction	1 (0.1)	0	0
Cardiac failure NOS	0	1 (1.2)	0
Myocardial infarction	0	1 (1.2)	1 (0.4)
Pneumonia NOS	0	1 (1.2)	0
Ventricular fibrillation	0	0	1 (0.4)

Source: Volume 87: Table 5.2-1. Includes: 103, 104, 106, 110

Table 12. Number of deaths by principal cause assessed by investigator (107)

Principal cause of death	Valsartan n (%)	Placebo n (%)
Total number of randomized patients	2511 (100)	2499 (100)
Total deaths	505 (20.1)	499 (20.0)
Sudden death—unespected, instantaneous or during sleep (observed or presumed)	194 (7.7)	177 (7.1)
Pump failure, progressive CHF even if terminal event was arrhythmia or vascular event	143 (5.7)	130 (5.2)
Other non-cardiovascular event	43 (1.7)	130 (5.2)
Sudden death-premonitory worsening, CHF	22 (0.9)	34 (1.4)
Non-cardiovascular event—cancer	20 (0.8)	24 (1.0)
Unknown	15 (0.6)	22 (0.9)
Other vascular event	15 (0.6)	24 (1.0)
Acute myocardial infarction – documented	14 (0.6)	11 (0.4)
Vascular event—stroke	13 (0.5)	6 (0.2)
Acute myocardial infarction—presumed	12 (0.5)	18 (0.7)
Sudden death—premonitory worsening, arrhythmia	6 (0.2)	13 (0.5)
Sudden death—premonitory	6 (0.2)	3 (0.1)

worsening, ischemia		
Vascular event—cardiac procedure	2 (0.1)	3 (0.1)

Source: Volume 77: Table 5-32

10.2. Serious Adverse Events

Table 13. Clinical Serious Adverse Events (Incidence ≥1.0 % for Valsartan Treatment Group and greater than placebo) in Double-blind controlled Studies, by Primary Term: Short-term*

Serious AE: Primary Term	Valsartan N=3282 n (%)	Active control N=86 n (%)	Placebo N=2740 n (%)
Total—any body system	548 (17)	11 (13)	490 (18)
Hypotension NOS	32 (1)	0	15 (0.5)

*Data from Studies 103, 104, 106, 107, 110 through visit 7.
Source: Volume 87: Table 5.2-4

Table 13a. Clinical Serious Adverse Events (Incidence ≥ 1.0 % for Valsartan Treatment Group and greater than placebo) in Long-term Placebo-Controlled (107) by Primary Term:

Serious AE: Primary Term	Valsartan N=2506 n (%)	Placebo N=2494 n (%)
Total: any body system	1282 (51)	1342 (54)
Angina pectoris	63 (3)	49 (2)
Dehydration	49 (2)	33 (1)
Hyperkalemia	40 (2)	23 (0.9)
Dizziness (exc vertigo)	39 (2)	36 (1)
Syncope	62 (3)	60 (2)
Renal failure NOS	25 (1)	15 (0.6)
Renal impairment	44 (2)	20 (0.8)

Source: Volume 87: Table 5.2-6.

The table below lists adverse experiences in the short-term controlled clinical trials. Only dizziness (exc. Vertigo) appeared to increase in frequency with increasing dose (2.3% in 0 mg, 7.7% in 80 mg BID, 7.4% in 160 mg BID, and 9.0% in 320 mg BID groups). The incidence of dizziness and hypotension NOS were statistically significant for valsartan compared to placebo. The incidence of cough was 4.9% in placebo and 4.8% in valsartan.

Table 14. Treatment Emergent Adverse experiences: double-blind short-term trials (Incidence ≥ 1.0 % in the valsartan group and greater than placebo)

Preferred term	Valsartan (N=3282) n (%)	Active control (N=86) n (%)	Placebo (N=2740) n(%)
Any—Total	2380 (73)	53 (62)	1876 (69)
Anemia NOS	43 (1)	0	23 (0.8)

Angina pectoris	76 (2)	1 (1)	58 (2)
Angina (combined)*	109 (3)	1 (1)	98 (4)
Cardiac failure congestive	34 (1.0)	0	20 (0.7)
Congestive heart failure (combined)**	153 (5)	1 (1)	165(6)
Vertigo NEC	60 (2)	2 (2)	26 (0.9)
Vision blurred	47 (1)	0	8 (0.3)
Diarrhea NOS	148 (5)	2 (2)	100 (4)
Fatigue	89 (3)	2 (2)	52 (2)
Weight increased	35 (1)	0	16 (0.6)
Hyperkalemia	79 (3)	0	29 (1)
Arthralgia	90 (3)	1 (1)	58 (2)
Epistaxis	32 (1.0)	0	18 (0.7)
Back pain	86 (3)	4 (5)	51 (2)
Dizziness (exc. Vertigo)	568 (17)	7 (8)	255 (9)
Dizziness postural	81 (3)	0	32 (1)
Syncope	60 (2)	0	34 (1)
Renal impairment NOS	58 (2)	1 (1)	19 (0.7)
Renal impairment and failure (combined)***	96 (3)	1 (1)	38 (1)
Hypotension NOS	218 (7)	0	65 (2)
Postural hypotension	68 (2)	0	20 (0.7)

Source: Volume 77: Table 5.1-1. Includes: 103, 104, 106, 110 and 107 through Visit 7. Each patient is counted once per preferred term and per total daily dose within each body system. Active control=ACE inhibitors (lisinopril and enalapril). Incidence $\geq$ 1% is rounded off to the nearest integer.

*sum total: angina pectoris, angina pectoris aggravated and angina unstable.

**sum total: cardiac failure NOS, cardiac failure aggravated, cardiac failure chronic, cardiac failure congestive, congestive cardiac failure aggravated.

***sum total: renal failure NOS, renal failure acute, renal failure aggravated, renal failure chronic, renal failure chronic aggravated, renal impairment NOS.

In 107, Dizziness and hypotension NOS are also seen in more frequently in the valsartan group. Congestive heart failure aggravated, reported in 11% of valsartan and 15.5% of placebo, was apparently a statistically significant difference.

Table 15. Treatment-emergent adverse experiences (107) long-term (incidence $\geq$ 1.0 % in valsartan and greater than placebo)

	Valsartan (N=2506) n (%)	Placebo (N=2494) n (%)
Anemia NOS	119 (5)	110 (4)
Arrhythmia NOS	39 (2)	31 (1)
Myocardial infarction*	89 (4)	78 (3)
Ventricular extrasystoles**	27 (1)	22 (0.9)
Vertigo NEC	78 (3)	51 (2)
Vision blurred	55 (2)	22 (0.9)
Diarrhea NOS	238 (10)	193 (8)
Fatigue	117 (5)	106 (4)
Malaise	24 (1)	21 (0.8)
Gastroenteritis NOS	43 (2)	25 (1)
Herpes zoster	27 (1)	22 (0.9)
Blood creatinine increased	54 (2)	27 (1)

Diabetes mellitus aggravated	29 (1)	18 (0.7)
Hyperglycemia NOS	62 (3)	55 (2)
Hyperkalemia	163 (7)	81 (3)
Hyperlipidemia NOS	42 (2)	29 (1)
Arthralgia	195 (8)	172 (7)
Back pain	145 (6)	122 (5)
Dizziness (exc vertigo)	627 (25)	451 (18)
Dizziness postural	92 (4)	54 (2)
Renal failure NOS	54 (2)	31 (1)
Renal impairment	135 (5)	76 (3)
Renal impairment or failure¶	256 (10)	166 (7)
Wheezing	26 (1)	13 (0.5)
Hypotension NOS	347 (14)	19 (0.8)
Intermittent claudication	35 (1)	19 (0.8)
Postural hypotension	95 (4)	48 (2)

Source: Volume 77: Table 5.1-3. Incidences $\geq$ 1 have been rounded off to the nearest integer.
*Note: in this population, the incidence of angina pectoris, angina pectoris aggravated and unstable angina were all respectively higher in the placebo groups.
**Note: in this population, the incidence of ventricular bigeminy, ventricular fibillation, and ventricular tachycardia were higher in the valsartan group by 0.1-0.2% .
¶ sum total: renal failure NOS, renal failure acute, renal failure acute on chronic, renal failure aggravated, renal failure chronic, renal failure chronic aggravated, renal impairment NOS

Table 16. Number (and percent) of patients who prematurely discontinued from study treatment due to adverse experiences (short-term double-blind studies) (≥ 1% for valsartan)

Preferred term	Valsartan (n=776)	Active control (n=86)	Placebo (n=246)
Total (any body system)	67 (9)	4 (5)	9 (4)
Dizziness (exc vertigo)	17 (2)	0	0
Hypotension NOS	19 (2)	0	0

Source: Volume 87: Table 5.1-41. Includes: 103, 104, 106 and 110. Active control combines lisinopril and enalapril groups.

One patient was discontinued from valsartan (320 mg BID) and none from the other groups because of angioneurotic edema; 4 patients were discontinued from valsartan—none from the other groups—because of renal impairment or failure.

Table 17. Number (and percent) of patients discontinued from trial treatment (incidence > 1% in valsartan) due to adverse experiences --Long-term trial (107)

	Valsartan N=2506 n (%)	Placebo N=2494 n (%)
Total—any body system	249 (10)	181 (7)
Dizziness (exc vertigo)	41 (2)	11 (0.4)
Renal impairment NOS	27 (1)	6 (0.2)
Renal failure or impairment*	45 (2)	14 (1)
Hypotension NOS	32 (1)	20 (0.8)

Source: Volume 87: Table 5.1-43. A patient is counted once per preferred term within each body system.
*sum total: renal failure NOS, renal failure acute, renal failure acute on chronic, renal failure aggravated, renal impairment NOS

Laboratory changes:

Table 18. Number (%) of patients with specified percent change from baseline to final visit for selected biochemistry variables (primary dataset)

	Valsartan n (%)	Active control n (%)	Placebo n (%)
Creatinine ≥ 50% increase	123 (4)	1 (1)	24 (0.9)
Uric Acid ≥ 50% increase	93 (3)	2 (3)	48 (2)
Potassium * ≥ 20% decrease ≥ 20% increase (to endpoint)	81 (3) 298 (10)	0 5 (6)	104 (4) 128 (5)
BUN ≥ 50% increase	506 (17)	4 (5)	169 (6)
SGPT ≥ 150% increase	33 (1)	2 (3)	26 (1)
SGOT ≥ 150% increase	11 (0.4)	0	10 (0.5)
Alkaline phosphatase ≥ 100% increase	17 (0.6)	1 (7)	14 (0.6)
Total bilirubin ≥ 100% increase	74 (3)	1 (7)	14 (0.6)
Glucose ≥ 50% decrease ≥ 50% increase	44 (2) 108 (5)	0 1 (7)	38 (2) 110 (5)
Sodium ≥ 5% decrease ≥ 7% increase	53 (2) 12 (0.4)	1 (1) 1 (1)	42 (2) 14 (0.5)
Calcium ≥ 10% decrease ≥ 10% increase	59 (2) 78 (3)	3 (20) 3 (20)	45 (2) 57 (2)

Source: Volume 77: Table 6-7. *excludes values ≥ 7.0 mEq/l.
Includes 103, 104, 106, 107 (first 4 months) and 110

Table 19. Number (%) of patients with specified change from baseline for selected biochemistry variables (107)

	Valsartan n (%)	Placebo n (%)
Creatinine ≥ 50% increase (to endpoint) ≥ 50% increase (any point)	N= 2480 163 (7) 362 (15)	N=2475 87 (4) 150 (6)
Uric Acid ≥ 50% increase (to endpoint) ≥ 50% increase (any point)	N=2318 112 (5) 235 (10)	N=2333 96 (4) 184 (8)
Potassium * ≥ 20% increase (to endpoint) ≥ 20% increase (any point)	N=2307 262 (11) 791 (34)	N=2295 160 (7) 479 (21)
BUN ≥ 50% increase (to endpoint) ≥ 50% increase (any point)	N=2480 609 (25) 1161 (47)	N=2475 389 (16) 661 (27)

Source: Volume 77: Table 6-8, 6-10. *excludes values ≥ 7.0 mEq/l.

Hematology: There were small mean decreases from baseline in hemoglobin and hematocrit levels for the valsartan groups.

Table 20. Number (%) of patients with hematology values exceeding specified % change from baseline limit to final test result (primary dataset)

	Valsartan n (%)	Active control n (%)	Placebo n (%)
Hemoglobin			
≥ 20% decrease	56 (2)	1 (1)	20 (0.8)
≥ 50% increase	3 (0.1)	0	2 (0.1)
Hematocrit			
≥ 20% decrease	67 (2)	0	5 (0.2)
≥ 50% increase	10 (0.4)	3 (4)	53 (2)
WBC			
≥ 50% decrease	12 (0.4)	0	30 (1)
≥ 50% increase	78 (3)	3 (4)	156 (6)
Absolute neutrophils			
≥ 50% decrease	49 (2)	0	30 (1)
≥ 50% increase	177 (6)	0	156 (6)

Source: Volume 77: Table 6-16. Includes: 103, 104, 106, 107 (first 4 months), 110. N= patients with baseline + at least one post-baseline value

Table 21. Number (%) of patients with hemoglobin/hematocrit values exceeding specified % change from baseline to final result (107)

≥ 20% decrease	Valsartan N=2313 n (%)	Placebo N=2328 n (%)
Hemoglobin	70 (3)	44 (2)
Hematocrit	85 (4)	57 (3)

Source: Volume 77: Table 6-17.

Table 22. Mean change from baseline in DBP and SBP at selected timepoints (107)

	Time	Valsartan N=2506			Placebo N=2494		
		n	Baseline mean	Mean (SD) change	n	Baseline mean	Mean (SD) change
Sitting SBP	6 months	2203	123.8	-5.8 (15.9)	2261	124.5	-1.9 (15.4)
	1 year	2018	123.9	-5.2 (16)	2093	124.9	-1.3 (15.9)
	2 years	1209	124	-5.6 (17.1)	1248	124.6	-2.4 (15.9)
	3 years	123	123.9	-3.4 (17.6)	130	124.1	-0.8 (18.5)
	Endpoint	2494	123.4	-7.1 (17.8)	2482	120.4	-3.7 (17.5)
Sitting DBP	6 months	2201	75.8	-4 (10)	2261	75.8	-1.4 (10)
	1 year	2017	75.8	-3.8 (10.1)	2093	76.1	-1.2 (10.1)
	2 years	1209	76.2	-4.5 (10.7)	1247	76.3	-2.5 (10.7)
	3 years	122	74.9	-5 (10.1)	130	75.1	-3.3 (10.1)
	Endpoint	2494	75.5	-4.7 (11)	2482	75.6	-3 (10.8)

Source: Volume 77: Table 7-1

Summary:

1. There was an increased discontinuation from valsartan treatment, compared to placebo, due to adverse events in clinical trials.
2. An increased incidence of dizziness, hypotension, renal impairment and hyperkalemia are seen with valsartan (compared to placebo). Increases in creatinine, potassium and BUN are also seen in the valsartan group compared to placebo. It is not known whether these increases translate into hospitalization (non-CHF) for valsartan.
3. Decreases in SBP and DBP are noted with valsartan compared to placebo.

Individual Study Reviews:

Study 102. An Open-Label, Placebo-Controlled, Dose Ranging Trial to Determine the Acute Central Hemodynamic Effects of CGP 48933 in Patients with Stable, Chronic, Congestive Heart Failure (Phase II) (Protocol date: September 30, 1992)

Source: NDA Volume 12 (Study Report and Tables), 13 (Protocol); no .xpt datasets were submitted.
Valsartan and CGP48933 will be used interchangeably in this review.
This study was jointly reviewed with B. Nhi Nguyen, Pharm.D.

Primary Objectives:

1. Evaluate, by right heart catheterization, central hemodynamic effects of single, open-label doses of CGP 48933 (valsartan) 10, 20, 40, 80 and 160 mg compared to placebo up to 24 hours after dosing, in patients with stable chronic congestive heart failure with a NYHA classification of III or IV.
2. Evaluate safety and tolerability of single open-label doses of CGP 48933 10, 20, 40, 80, and 160 mg in patients with stable chronic congestive heart failure.

Secondary Objectives:

1. Obtain preliminary information on correlation between plasma levels of CGP 48933 and its acute central hemodynamic effects compared to placebo.
2. Obtain preliminary information on effects of CGP 48933 on plasma renin activity, plasma aldosterone, and plasma angiotensin II concentration up to 24 hours after dosing, compared to placebo, and correlate these effects with its acute hemodynamic actions.

Sites: 3 centers in the US.
Duration: March 12, 1993 (first patient, first visit) to April 4, 1994 (last patient, last visit)

Study Design:

This was a single-dose, open-label, randomized parallel-group study in patients with Class III or IV CHF. Chronic CHF medications were allowed until 2 days prior to dosing; at that time, ACE inhibitors, vasodilators and inotropic agents (except digoxin) were discontinued. On the day of dosing, diuretics were held and digoxin was allowed; antiarrhythmics were allowed throughout the study. Patients were to fast 9 hours prior to dosing. Randomized patients underwent right heart catheterization, via Swan-Ganz catheter, as well as arterial cannulation. After stable baseline hemodynamic measurements, patients were given a single dose of drug or placebo, and central hemodynamic and neurohormonal measurements were taken at 1, 2, 3, 4, 6, 8, 12, and 24 hours post dosing. After all measurements were taken, the lines were removed, patients resumed their prior medications, and were discharged to follow-up one week after dosing.

Figure 102.1. Treatment algorithm

		CGP 48933 10 mg (N=5) CGP 48933 20 mg (N=4) CGP 48933 40 mg (N=3) CGP 48933 80 mg (N=4) CGP 48933 160 mg (N=5) Placebo (N=4) ⇓		N=number randomized	
Visit	**1**	**2**	**3**		**4**
Day	**-14 to –3**	**-1**	**0**	**1**	**7**
Hour			**0**	**24**	

Inclusion Criteria [1]	Exclusion Criteria
• Male or female patients 18 to 80 years. • Chronic stable CHF, present for at least 4 weeks, NYHA Class III or IV, and ejection fraction ≤ 35%, determined by MUGA (determined up to 6 weeks prior to enrollment if interval-free of intercurrent events). Patients on background therapy should be on stable doses for at least 2 weeks prior to entry into the trial. • Must be able to tolerate discontinuation of ACE inhibitors, vasodilators, and positive inotropes (except digoxin) for 3 days and diuretics for 24 hours.	• Female patients of childbearing potential. • History of acute MI, unstable angina, acute pulmonary edema, or hospitalization for decompensated CHF within 4 weeks prior to entry into study. • Angina pectoris requiring more than 5 tablets/week of prn sublingual nitroglycerin. • Clinically significant primary valvular dysfunction. • Presence or history of restrictive cardiomyopathy, constrictive pericarditis, dyspnea of non-cardiac origin, gastrointestinal disease or surgery which would impair drug absorption, any condition/lab abnormality which would interfere with this study. • Complex or life-threatening ventricular arrhythmias. • Clinically signficant renal, hepatic, or hematologic disorders, unless consistent with CHF. • Uncontrolled hypertension (BP ≥ 160/100). • Unstable insulin-dependent diabetes mellitus. • Presence/recent serious psychiatric disorder, personality problem or living condition suggesting that the patient would be unable to participate fully in this trial. • Inability to discontinue long-acting nitrates, positive inotropes, vasodilators, beta blockers, calcium channel blockers, ACE inhibitors and diuretics.

Randomization criteria (patients must meet all criteria in order to be randomized):

1. All baseline hemodynamic measurements were to be repeated at 20 minute intervals until 2 consecutive sets of heart rate (HR), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) measurements were within 10%, respectively. A maximum of 5 sets of measurements were to be done. If the fifth set of measurements was not within 10% of the fourth set, then the patient was to be discontinued from the trial.
2. The patient was to be clinically stable (i.e., no complications from Swan-Ganz or arterial cannula insertion, or change in any concomitant condition).
3. PCWP on the second set of measurements had to be ≥ 15 mm Hg.

Sample Size: A total of 36 evaluable patients, defined as those who satisfied entry criteria and completed all visits. There was no sample size calculation.

[1] Taken from Protocol. Please see Amendments to the Protocol for changes in Inclusion/Exclusion criteria.

Primary Efficacy Variable :
Change from baseline in PCWP and CO measured at 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing.

CO was determined by taking 5 measurements, excluding highest and lowest values, and averaging the remaining 3 values.

Secondary Efficacy Variables:
1. Change from baseline in right atrial pressure (RAP), diastolic, systolic and mean pulmonary artery pressure (PAP),CI, SVR, PVR, SVI, heart rate, and systolic, diastolic and mean systemic blood pressure (MAP) measured at 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing.
2. Change from baseline, compared to placebo, in plasma renin activity, plasma aldosterone and plasma angiotensin II activity measured at 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing.
3. CGP 48933 blood levels at 1, 2, 3, 4, 6, 8, and 12 hours after dosing.

CI, SVR, SVI, and PVR were calculated from formulas that were prespecified in the protocol.

Statistical Plan: There were no prespecified statistical analyses or interim analysis.

Safety Variables: Physical examination (all visits), body weight (all visits), adverse experiences, laboratory testing (CBC, chemistry, urinalysis at Visits 1, 2, 3, 4), 12-lead ECGs (Visits 1 and 3), CXR(Visit 1), MUGA scan (within 6 weeks of Visit 1 or before Visit 2).

Laboratory: Central laboratory (National Health Laboratory).

Amendments to the Protocol (not signed):
1. (not dated) Under "presence of clinically significant renal, hepatic, or hematologic disorders" Specified exclusion criteria of hemoglobin < 10 g/dl.
2. (not dated). Changed entry criteria to "patients who are clinically stable for one week prior to entry into the trial" with stable background medications for 1 week prior to discontinuation of ACE inhibitors and diuretics.

Drug Supply : Drug Supply was provided by Ciba-Geigy. Batch and formulation numbers are as follows:

Table 102.1. Supply batch and formulation numbers

Treatment group	Batch Number	Formulation Number
Valsartan 10 mg	E-14937	H-3573
Valsartan 20 mg	E-14938	H-3574
Valsartan 40 mg	E-14939	H-3575
Valsartan 80 mg	E-14940	H-3576
Valsartan 160 mg	E-14941	H-3577
Placebo	E-14942	H-3577

Source: Sponsor: Volume 12 (Study report)

Medication was started on Visit 3 (Day 0) after all baseline measurements. All doses were administered in the fasting state with direct supervision.

Assay:
The assay used was precise, accurate, sensitive and linear over the concentrations of 5 – 3000 ng/mL (see table below). Plasma valsartan concentrations were determined by a validated HPLC method. The analysis was done at the laboratories of Bioanalytics and Pharmacokinetics, Rueil-Malmaison, France from January 24, 1994 to March 18, 1994.

Table 102.2. Quality of assay

	Precision (%)	Accuracy (%)	Sensitivity (ng/mL)	Linearity (ng/mL)
Valsartan	CV < 18%	Within 5%	5.00 – 3000	0.9987

Results:

Patient Disposition:
Thirty two patients were enrolled at Visit 1; seven patients were discontinued prior to randomization (6 did not meet protocol criteria and 1 withdrew consent). Twenty-five patients were randomized at Visit 2 and all completed the study; all were included in efficacy and safety analyses.
Of the baseline characteristics, all were NYHA Class III.

Protocol violations: A total of 6 randomized patients were noted to have protocol violations related to entry criteria. These included: consecutive PCWP not within 10% (Valsartan 40:1 patient); HR measurements not within 10% (Valsartan 80: 1 patient; Valsartan 160: 1 patient); inducible VT (Valsartan 10: 1 patient); screening visit ejection fraction of 36% (Valsartan 160 mg: 1 patient); woman of childbearing potential (valsartan 40: 1 patient).

Baseline characteristics:
As seen in the table below, this was a mostly male population with a small sample size per treatment arm. Of note, mean baseline PCWP were not uniform, with a higher baseline in the placebo group; hence, interpretations of changes from baseline will be confounded by these baseline differences in the treatment groups.

There are also baseline differences between treatment groups in mean weight, duration of CHF, plasma renin activity as well as plasma aldosterone.

Table102. 3. Baseline characteristics

	Placebo N=4	10 mg N=5	20 mg N= 4	40 mg N=3	80 mg N=4	160 mg N=5
Male (%)	4 (100)	3 (60)	4 (100)	2 (67)	4 (100)	5 (100)
Race: Caucasian	2(50)	2 (40)	1 (25)	0	0	1 (20)
Black	2 (50)	3 (60)	3 (75)	3 (100)	4 (100)	4(80)
Mean age (±SD)	48 (10)	44 (12)	54 (9)	50 (10)	55 (15)	54 (13)
Mean weight (lbs)	202 (32)	170 (26)	200 (53)	167 (51)	216 (53)	152 (17)
Mean duration CHF (yrs)	4 (3)	5 (4)	7 (2)	4 (2)	3 (2)	4 (4)
Etiology: Ischemic	1 (25)	1 (20)	1 (25)	0	2 (50)	2 (40)
Idiopathic	1 (25)	2 (40)	1 (25)	2 (67)	2 (50)	1 (20)

Hypertensive	1 (25)	0	2 (50)	0	0	2 (40)
Other	1 (25)	2 (40)	0	1 (33)	0	0

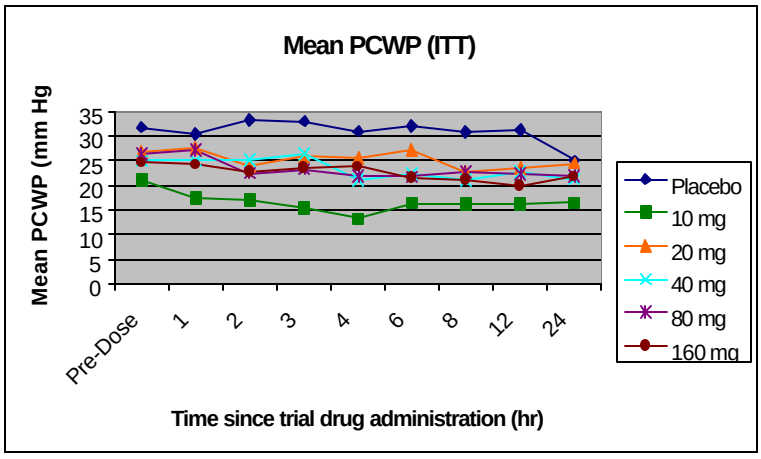
Table 102.3. Baseline characteristics (cont.)

	Placebo N=4	10 mg N=5	20 mg N= 4	40 mg N=3	80 mg N=4	160 mg N=5
Mean Baseline* PCWP (mm Hg) (+ SD)	31.8 (5)	21.0 (8)	26.8 (7)	25 .0(7)	26.5 (6)	24.6 (8)
Mean Baseline* CO (l/min) (+ SD)	3.9(1)	4.2 (1)	3.6(0.6)	4.1 (0.5)	4.0 (1)	4 (0.9)
Mean Baseline* plasma renin activity	6.1(6)	3.1 (4)	2.6 (3)	0.2 (0.2)	3.8 (3)	3 (6)
Mean baseline* plasma Aldosterone	12 (12)	6 (7)	13 (5)	8 (4)	6.8 (4)	17.2 (29)
Mean baseline* plasma Angiotensin II	34.3 (12)	30.6 (20)	31 (22)	27 (8)	48 (31)	34.4 (18)

Source: Volume 12: Tables 7.1:1, 7.1:2, , 8.1:1A, 11.1:2A *Baseline =Pre-Dose value

Primary efficacy variable:
Figures 102.2-5 show the primary efficacy variables, including change from baseline, over time. The placebo group, with the highest mean value at baseline, also shows the largest decrease at 24 hours. A dose-response relationship was not seen.

Figure 102.2. PCWP over time (ITT)



Source for Figures 2 and 3: Volume 12: Tables 8.1:1A, 8.1:1B

Figure 102.3. Change from baseline in PCWP

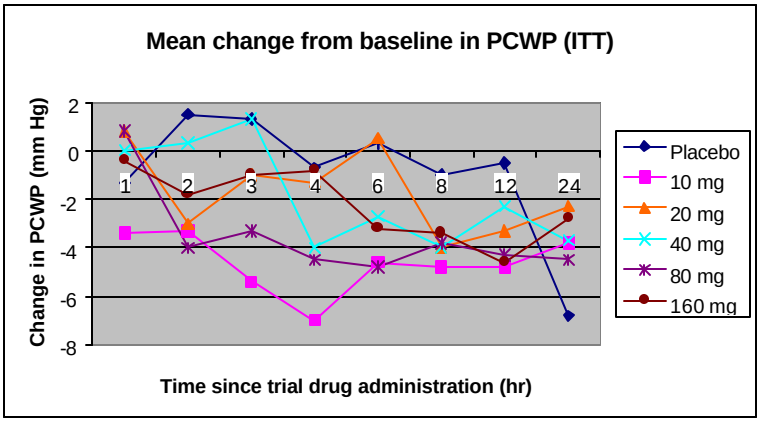
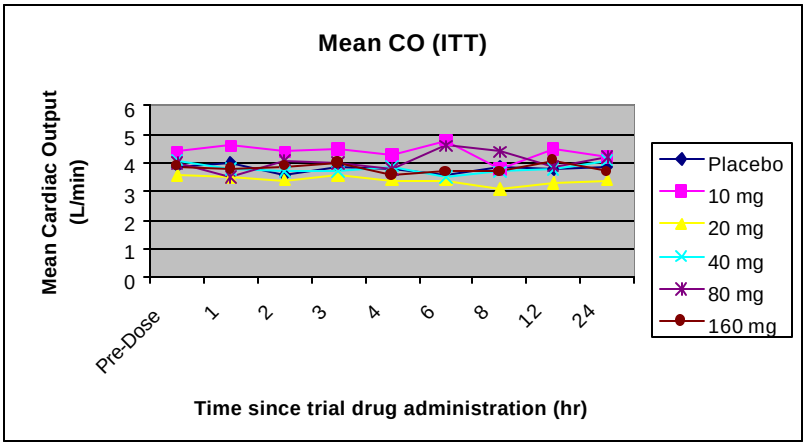


Figure 102.4. Cardiac Output (CO) over Time (ITT)



Source for Figures 4 and 5: Volume 12: Tables 8.1:1A and 8.1:1B

Figure 102.5. Change from baseline in Cardiac Output (ITT)

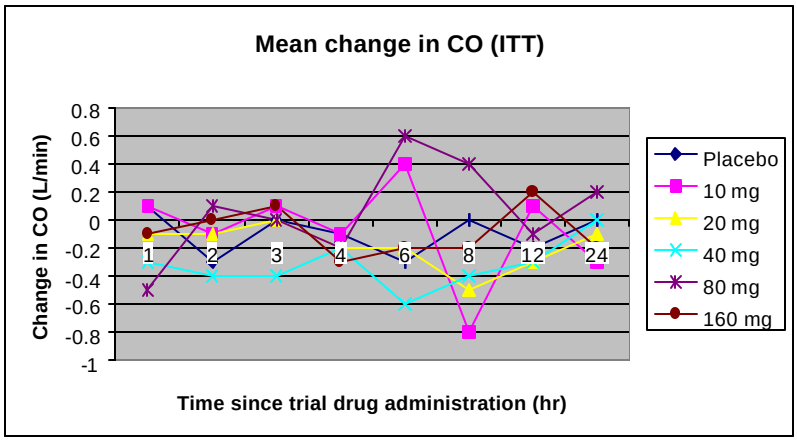


Table102. 4. Primary Efficacy Variables: Change from Baseline at 24 hours (ITT)

	PCWP	CO
	Change from baseline at 24 hours	Change from baseline at 24 hours
Placebo	-6.8 (2.4)	-0.04 (1.4)
Valsartan 10 mg*	-3.8 (3.3)	-0.3 (0.8)
Valsartan 20 mg	-2.3 (7.4)	-0.1 (0.8)
Valsartan 40 mg	-3.7 (2.1)	-0.03 (0.6)
Valsartan 80 mg	-4.5 (6.9)	0.2 (0.9)
Valsartan 160 mg	-2.8 (7.0)	-0.2 (1.5)

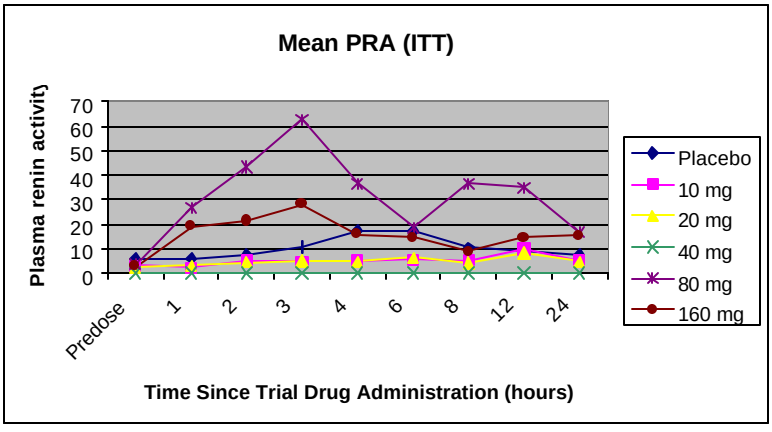
Source: Volume 12: Study Report and Table 8.1:1B * patient 11/507 did not have 24 hour efficacy measurements and was not included in this table.

The above table shows change from baseline at 24 hours for both primary efficacy variables. For PCWP, the placebo group had the highest pre-dose values and showed the largest change from baseline at 24 hours.

Secondary efficacy variables: The secondary efficacy variables were reviewed. No dose-response relationship or significant changes from baseline compared to placebo could be ascertained; this result may be due in part to the small sample size as well as baseline differences. Therefore, these data will not be presented.

Neurohormone results:
Neurohormone results over time are represented in the next figures. It should be noted that the valsartan 40 mg group, unlike the other groups, shows unusually flat neurohormonal responses. There appear to be elevations in plasma renin activity and angiotensin II at the higher doses, although a clear dose-relationship is not seen.

Table 102.6. Plasma Renin Activity (PRA)



Source for Figures 6 and 7: Volume 12: Table 11.1:2A, 11.1:2B

Figure102. 0-7. Change from baseline in Plasma Renin Activity (PRA)

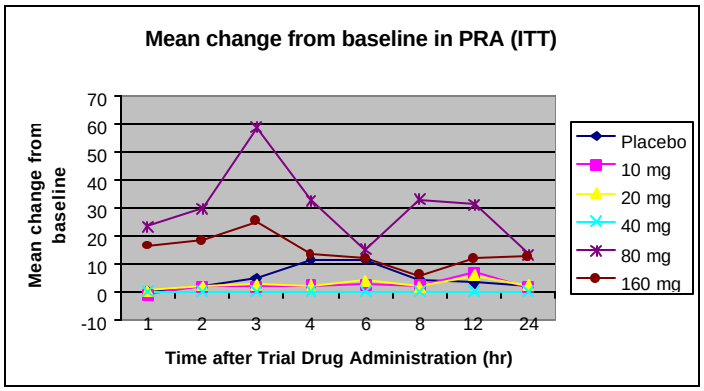


Figure 102.0-8. Plasma Angiotensin II

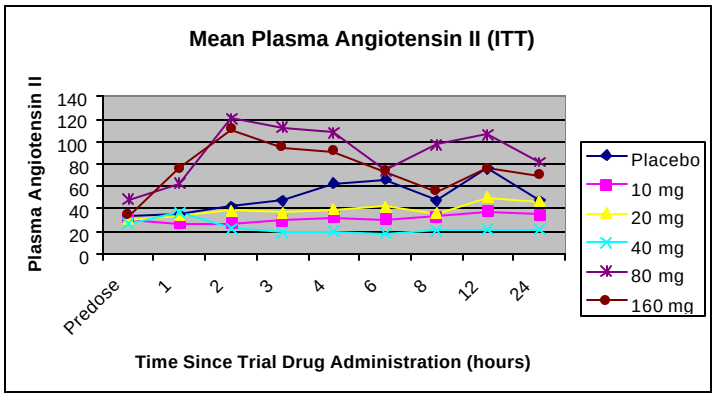
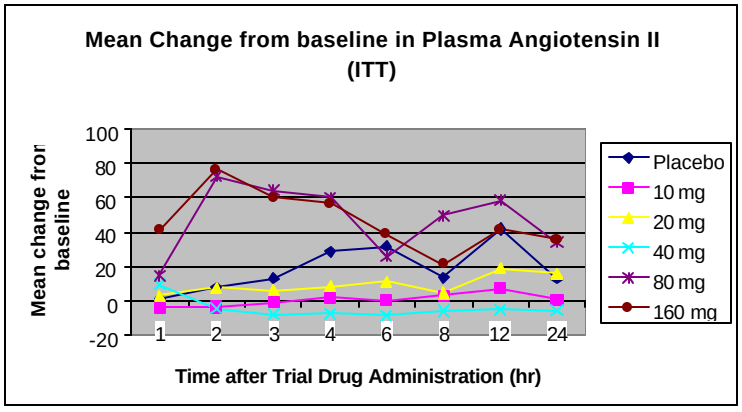


Figure 102.0-9. Change from baseline in Angiotensin II



Source: Volume 12: Tables 11.1:2A and B

Figure 102.0-10.Plasma Aldosterone

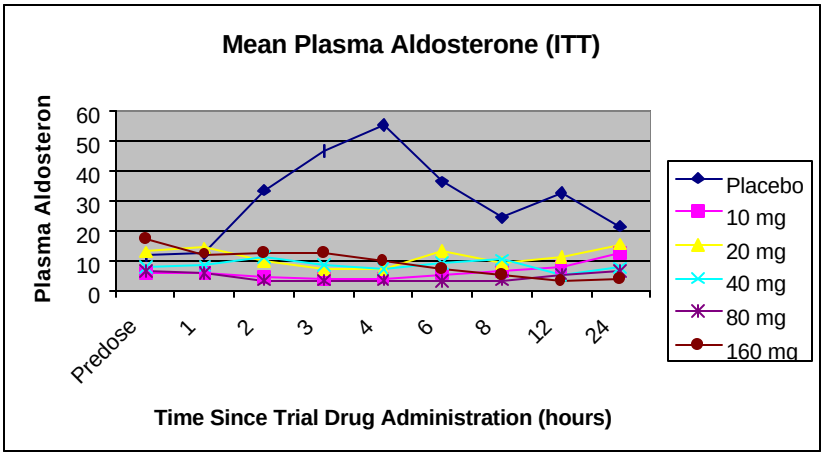
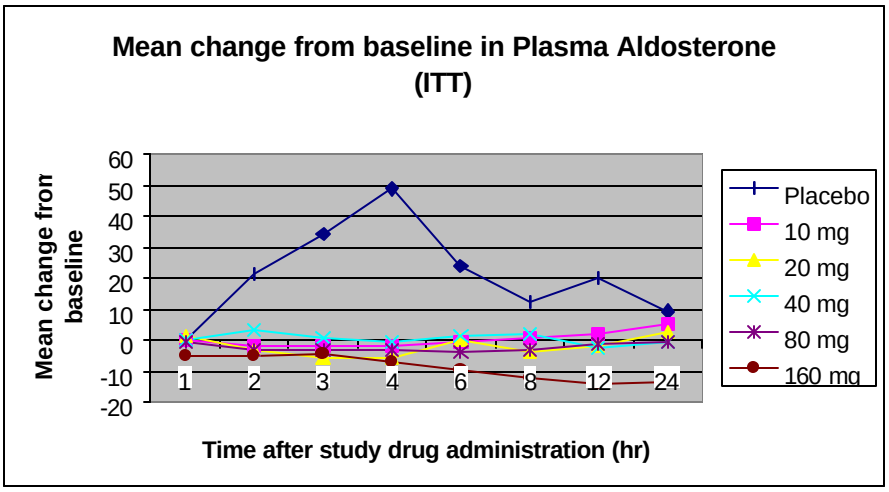


Figure 102.0-11. Change from Baseline in Plasma Aldosterone



Pharmacokinetic/pharmacodynamic results

The pharmacokinetic data are highly variable (see table 102.5). Cmax was reached ~ 3 hours after dosing.

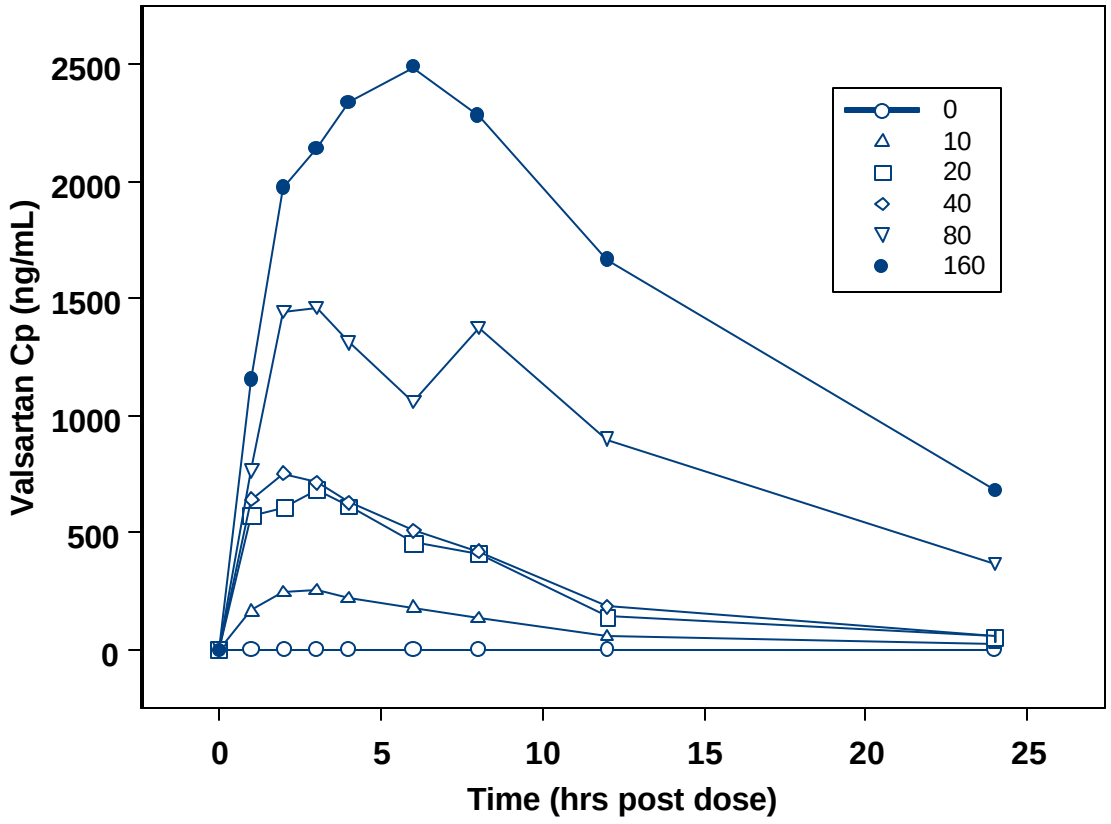
Table 102.5 . Mean pharmacokinetic parameters

Dose (mg)	N	Cmax (ng/ml)			Tmax	(hr)	AUC (0-24 hr) ng x hr/ml		
		Mean	SD	CV (%)	Median	Range	Mean	SD	CV (%)
10	5	280	68	24	3	2-6	2380	370	16
20	2	684	149	22	2.5	2-3	6380	2750	43
40	3	843	308	36	2	1-8	7150	1430	20
80	4	2150	1490	69	3	2-8	21200	18900	89
160	4	2770	1130	41	6	1-6	38000	25000	66

Source: Sponsor: Volume 12: Study Report

Valsartan exhibits a 2-compartment pharmacokinetic model as shown by the shape of the plasma concentrations time curves in Figure 102.012.

Figure 102.012. Valsartan plasma concentration vs. time after single dose



Individual Cmax and AUC were fitted using NONMEM (ver 5.0, level 1.1) to the following equation:

$$Y = \alpha * Dose^{\beta}$$

where Y is the predicted Cmax or AUC, α is the slope of the fit and β determines the linearity of the fit. The parameter estimates are shown in Table 9.

Single doses of valsartan are dose proportional over the range of 10 mg to 160 mg. βeta for both Cmax and AUC are close to one, suggesting that valsartan exhibits linear pharmacokinetics over the concentration range of 0-2500 ng/mL. The 95% confidence interval for Cmax is (0.732, 1.128) and for AUC is (0.962, 1.258). The residual error estimation is ~43% and ~50% for Cmax and AUC, respectively, implying that a considerable portion of the variability is unexplained by the model. Although valsartan exhibits linear pharmacokinetics, it should be noted that the pharmacokinetics are quite variable.

Table 102.6 . Summary of model parameter estimates

	Cmax (ng/mL)		AUC (ng*hr/mL)	
	a	**b**	**a**	**b**
Mean	31.9	0.93	165	1.11
SE (%)	26.3 %	9.4	27.6 %	8.4 %
Residual error (CV%)	42.5 %		50.5 %	
SE (%)	28.2 %		30.0 %	

I.

Figure 102.013. Observed and predicted AUC at 5 different doses

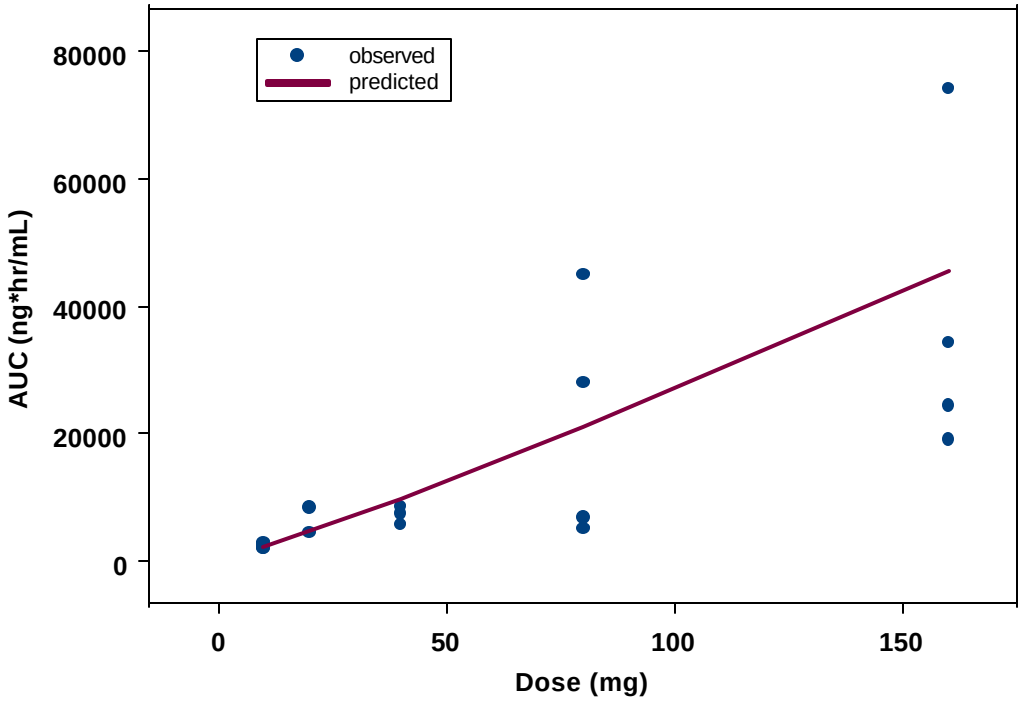
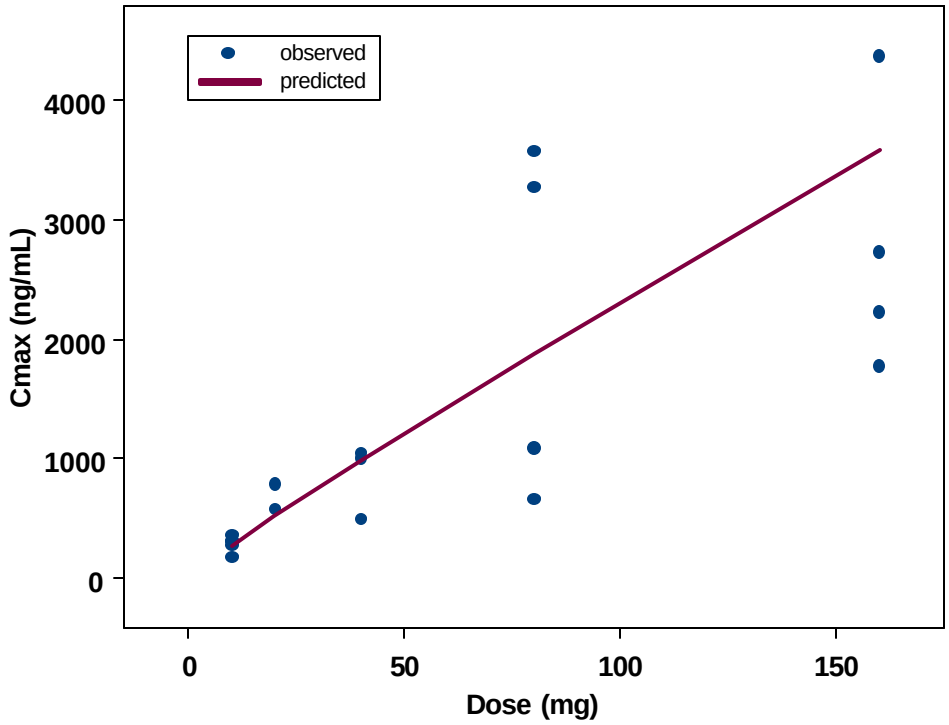


Figure 102.0-14. Observed and predicted Cmax at 5 different doses



There was not an evident PK/PD relationship with PCWP or CO.

Figure 102-0.15. Mean PCWP and valsartan concentration relationship

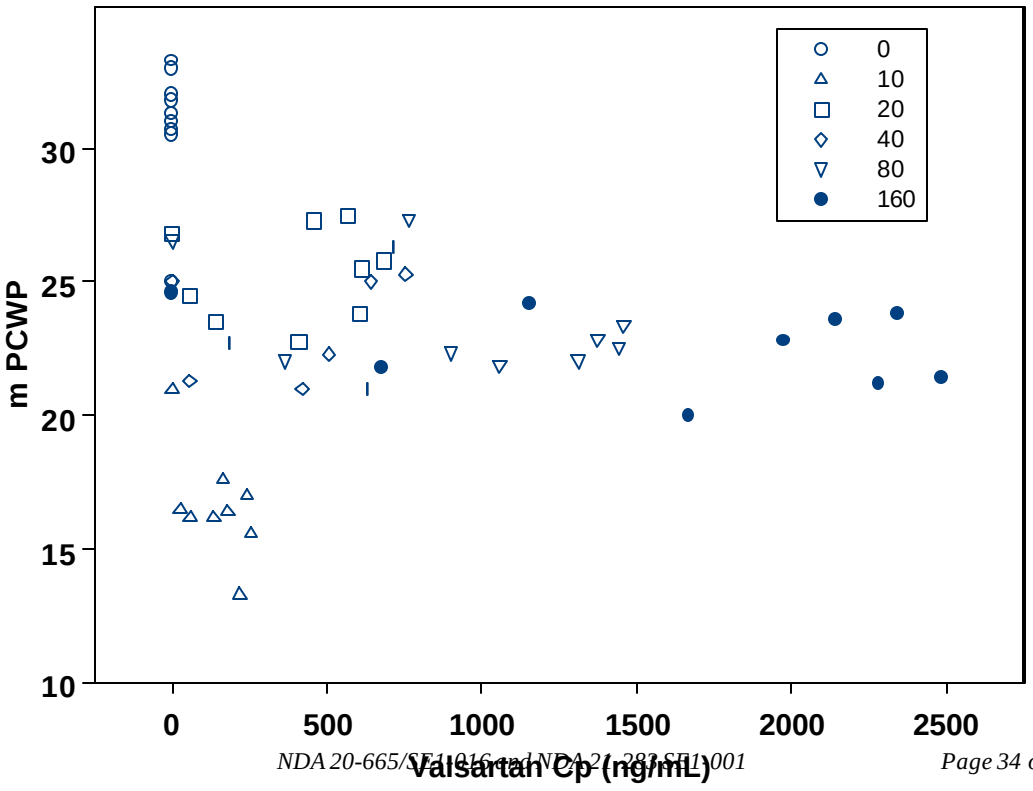
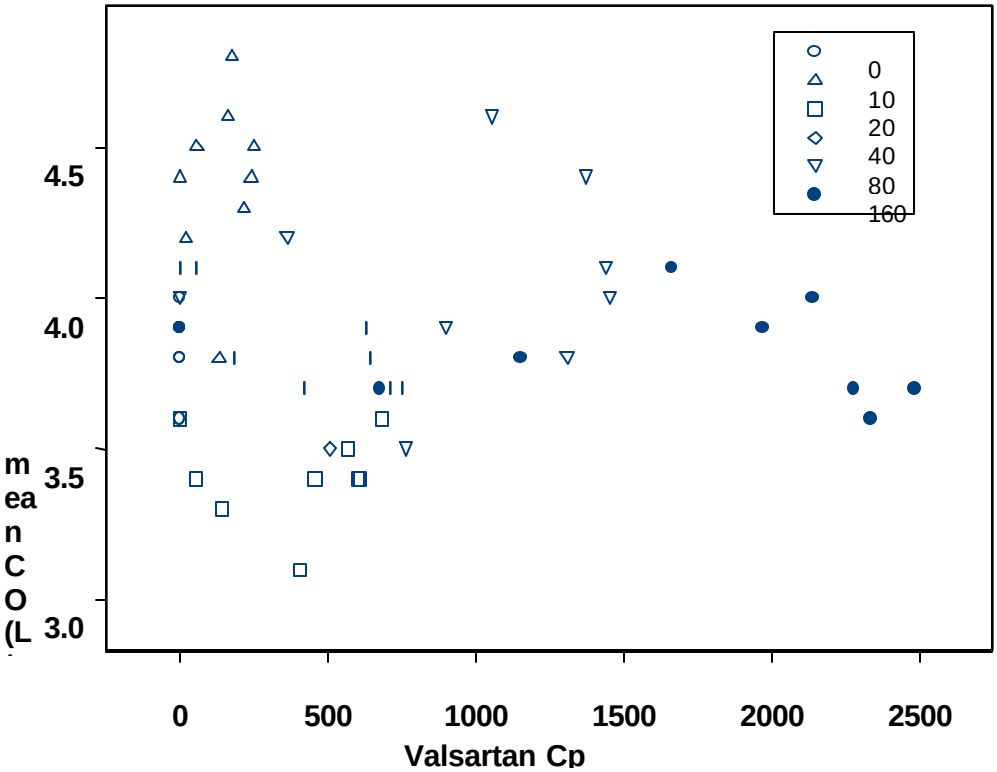


Figure 102.0.16. Mean CO and valsartan concentration relationship



There was a slight trend in the placebo-adjusted change from baseline PRA, aldosterone and angiotensin II (see figures 102.0-17, 18, and 19).

Figure 102.0-17

PK/PD relationship for plasma renin activity

Plasma valsartan concentration (ng/mL) vs. placebo adjusted change from baseline for plasma renin activity (ng/mL/hr) following a single 10 mg to 160 mg doses of valsartan in CHF patients.

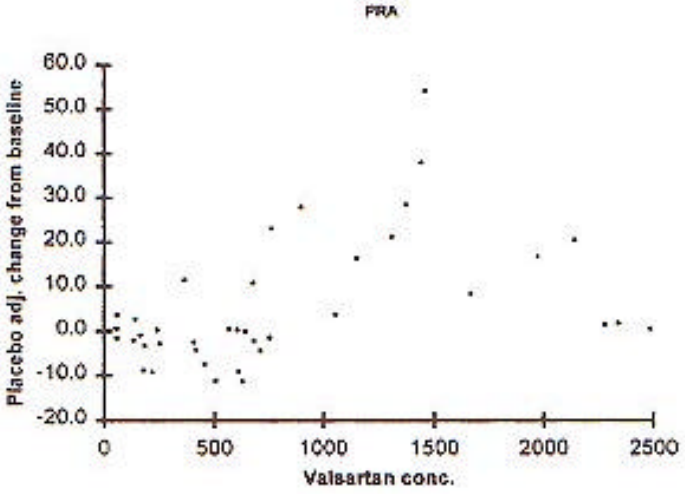


Figure 102.0-18.

PK/PD relationship for plasma aldosterone concentration

Plot of plasma valsartan concentration (ng/mL) vs. placebo adjusted change from baseline for plasma angiotensin II (Ang II) concentration (ng/L) following a single 10 mg to 160 mg doses of valsartan in CHF patients.

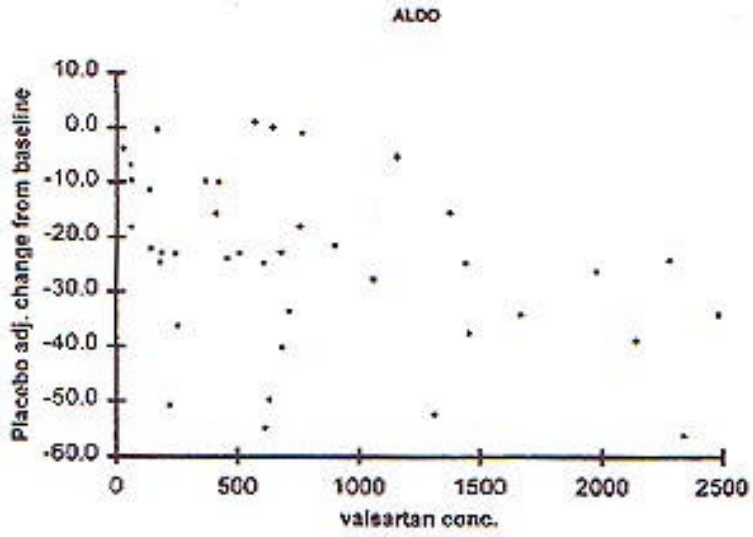
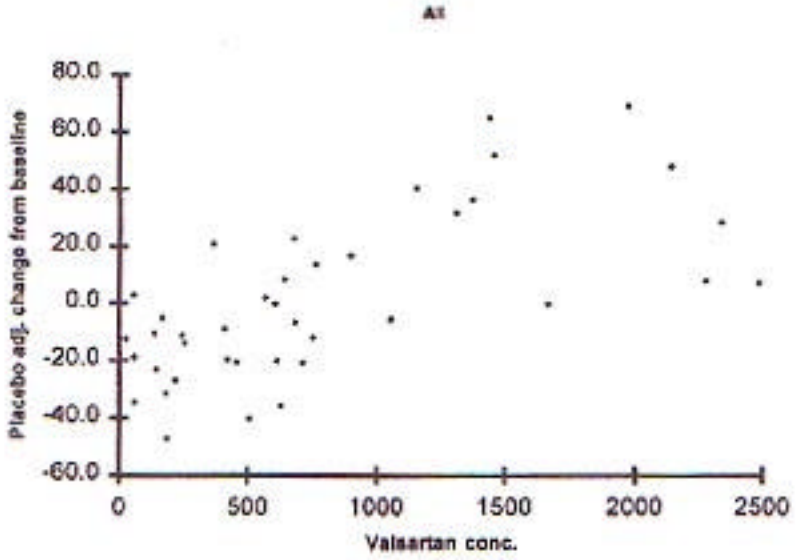


Figure 102.0-19

PK/PD relationship for plasma angiotensin II concentration

Plasma valsartan concentration (ng/mL) vs. placebo adjusted change from baseline for plasma angiotensin II (Ang II) concentration (ng/L) following a single 10 mg to 160 mg doses of valsartan in CHF patients.



Safety

There were no premature discontinuations after randomization. There were no deaths during this trial.
Out of 25 randomized patients, 10 (8 on valsartan, 2 on placebo) reported adverse experiences.

There was one serious adverse experience (deterioration in CHF). A 65 year old 81 kg male with Class III CHF, randomized to valsartan 160 mg, was admitted to the CCU, 24 hours after dosing with trial medication, for IV infusions of dopamine (2mcg/kg/min) and dobutamine (10 mcg/kg/min). After 27 days, the patient was discharged with adjusted medications.

Table 102.7. Treatment-emergent adverse experiences (occurring in at least 2 patients on valsartan)

(all randomized patients)

Adverse event by primary term	Placebo (n=4) n (%)	Total valsartan (n=21) n (%)
Deterioration of basic disease	0	2 (9.5)
Dizziness	0	3 (14.5)

Source: Volume 12, Table 9.1:5

For further discussion, including evaluation of laboratory results, please see the Integrated Summary of Safety.

Medical Reviewer's Comments:
This was a small, single-dose open-label study investigating hemodynamic and pharmacokinetic effects with valsartan compared to placebo. The small sample size, as well as baseline differences between the treatment groups, limit interpretation of the data. No dose-response pattern could be seen in reviewing the hemodynamic data.

PK Reviewer's Comments:
Valsartan exhibits linear pharmacokinetics over the concentration range of 5-2,500 ng/mL. However, the data are highly variable. The linearity is consistent with previous reports in healthy volunteers. Tmax, ~3 hours, is also similar to previous reports. T ½ seems to be longer in patients with CHF than in healthy volunteers (median of ~9 hours compared to ~6 hours, respectively.) However, only two plasma samples were taken after 10 hours in this single dose study, so the T ½ may be inaccurate.

There was a weak trend towards an increase in placebo adjusted mean change from baseline for PRA and Ang II, and a decrease in aldosterone concentrations with increasing valsartan concentrations. However, no definitive conclusions regarding these trends can be made from this study.

Medical Reviewer's Conclusions:
No efficacy conclusions will be drawn given the limited data. Valsartan appeared to be well tolerated in this study.

PK Reviewer's Conclusions:
Valsartan exhibits 2-compartment linear pharmacokinetics over the concentration range of 5 to 2,500 ng/mL (doses of 10 mg to 160 mg).

Single doses of valsartan in this small patient study do not show an apparent concentration response relationship with respect to PCWP and CO.

Study 103. A multicenter, double-blind, randomized, placebo- and active-controlled, between patient trial to assess the cardiac hemodynamic effects of valsartan 40 mg, 80 mg and 160 mg, all twice daily, in patients with chronic stable congestive heart failure NYHA stage II-IV treated for four weeks (Phase II) (Protocol date: January 25, 1995

Source: NDA Volume 65 (Study Report and Tables), 67 (Protocol); electronic (.xpt) datasets.

Primary Objective (listed as "aim" in the protocol):

- Assess the cardiac hemodynamic effects of valsartan 40 mg, 80 mg and 160 mg, all twice daily, in patients with chronic stable congestive heart failure NYHA stage II-IV after four weeks of treatment.

Secondary Objective (listed as "aim" in the protocol):

- Evaluate safety and tolerability of valsartan administered to patients with stable chronic congestive heart failure.

Sites: This 9 site study was conducted in Russia. The principal investigator was Dr. Vladimir Mazayev, MD, DMSc.

Duration: April 14, 1995 (first patient, first visit) to March 38, 1996 (last patient, last visit)

Study Design:
This was a multicenter, double-blind, randomized study in patients with chronic stable Class II-IV CHF. After a 2-4 week drug-free run-in period, eligible patients were randomly assigned, with a ratio of 2:2:2:2:1 to receive either valsartan 40 mg, 80 mg, 160 mg, placebo (all BID) for 4 weeks or lisinopril 5 mg QD (1 week) followed by lisinopril 10 mg QD (3 weeks) to complete 4 weeks of treatment. Treatments were matched to look identical in size and color; lisinopril was given as active treatment in the morning with a matching placebo in the evening for a twice daily regimen.

Figure 103.0-1. Study design

Enrollment Run-in Period		Randomization Valsartan 40 mg BID Valsartan 80 mg BID Valsartan 160 mg BID Placebo Lisinopril 5 mg ⇒10 mg QD (Visit 3) ⇓ ⇓			
Visit Day **Hour**	**1** **-28 or –14**	**2** **-1to 1**	**3** **7** **0**	**4** **14**	**5 (Final)** **27-28**

On Day –1 (Visit 2) patients were admitted for right heart catheterization. Patients were eligible for randomization if the initial two mean pulmonary capillary wedge pressures (PCWP) were both ≥ 18 mm Hg. A maximum of 5 sets of measurements (each set containing two

measurements) was to be done. If the fifth mean PCWP was not within 10% of the fourth, the patient was to be discontinued from the trial. The same procedures were to be followed for Visit 5 (day 27-28). Hemodynamic measurements were to be taken at 0.5, 1, 2, 3, 4, 6, 8 and 12 hours post-dose.

Inclusion Criteria [2]	Exclusion Criteria
• Male or female patients 18 to 80 years, inclusive. • Symptomatic chronic stable CHF, present for at least one month prior to Visit 1, NYHA Class II, III or IV. • Mean PCWP $\geq$ 18 mm Hg[3] at rest at Visit 2 (Day –1) • Written informed consent to participate in the trial and to attending the examinations laid out in the protocol.	• Pregnancy, nursing, or women of childbearing potential without an effective method of birth control. • History of acute MI, unstable angina, acute pulmonary edema, or hospitalization for decompensated CHF within 3 months prior to Visit 1. • Angina pectoris requiring more than 15 tablets/week of prn sublingual nitroglycerin. • Clinically significant primary valvular dysfunction (except mitral regurgitation secondary to a dilated failing LV). • Presence or history of restrictive cardiomyopathy, constrictive pericarditis. • Dyspnea of non-cardiac origin within the past year. • Gastrointestinal disease or surgery which would impair drug absorption, any condition/lab abnormality which would interfere with this study. • Life-threatening ventricular arrhythmias including arrhythmias requiring cardioversion or AICD or episodes of symptomatic sustained VT lasting longer than 30 seconds at any time previous to or during the trial, or requirement of antiarrhythmic agents affecting myocardial performance at usual doses (eg calcium antagonists, beta blockers, flecainide, disopyramide). • Hepatic disease as determined by: SGOT or SGPT > two times ULN, history of hepatic encephalopathy, esophageal varices, portocaval shunt. • Renal impairment as determined by: serum creatinine $\geq$ 1.5 times ULN or history of dialysis. • Uncontrolled hypertension (BP $\geq$ 160/100 mm Hg) or malignant hypertensive or Keith-Wagner Grade III or IV hypertensive retinopathy. • Hypotension (BP < 80/50 mm Hg). • Hypertensive encephalopathy or CVA within past 6 months. • Clinically significant allergies or multiple drug allergies.

[2] Taken from Protocol. Please see Amendments to the Protocol for changes in Inclusion/Exclusion criteria.
[3] Please see Protocol amendment: this criteria was lowered to $\geq$ 15 mm Hg.

	• IDDM. • NIDDM with poor glucose control, peripheral neuropathy or autonomic neuropathy. • Malignancy (exc. for basal cell CA) within past 5 years. • History of any other severe life-threatening disease. • Administration of ACE inhibitors 6 months prior to Visit 1. • Drug/alcohol abuse within the past 2 years. • Participation in any investigational drug trial within 30 days prior to Visit 1. • Those persons directly involved in the execution of this protocol.

Allowed Concomitant medications:

- Digitalis (administered prior to 12 hour hemodynamic measurement, where applicable)
- Diuretics
- Long-term oral anticoagulant therapy
- Acute use of medications (e.g., antibiotic or analgesic use)

Excluded medications:

- Daily doses of diuretic greater than 80 mg furosemide or equivalent.
- Administration of diuretic on Days –1, 0, 27 and 28.
- Administration of nitroglycerine 12 hours prior to hemodynamic measurements.
- Antihypertensive agents except for diuretics.
- Vasodilator drugs (e.g. hydralazine and long-acting nitrates).
- Calcium antagonists.
- Tricyclic antidepressants.
- MAO inhibitors.
- Phenothiazines.
- Anti-inflammatory drugs, both steroidal or nonsteroidal. Topical steroids were allowed.
- Thyroid medication unless this has been a stable maintenance replacement dose for the preceeding 6 months.
- Over the counter diet preparations.
- Common cold preparations taken chronically.
- Amphetamine and its derivatives.

Table 103.1 . Schedule of Procedures

Period	Drug-free run-in period	Double-blind treatment period			
Visit	1	2	3	4	Final
Day	-28 (-14)	-1 to 1	7	14	27-28
History/ECG/CXR/Informed consent	X				
Physical exam/signs and symptoms of CHF/weight/pulse/BP	X	X	X	X	X
Inclusion/Exclusion criteria	X	X			
Routine laboratory tests	X	X		X	X
Right heart catheterization; 12 h hemodynamics		X			X
Withhold diuretics		X (day-1, day 0)			X (day 27, 28)
Withhold NTG 12 hours prior to hemodynamic measures		X (day-1, day 0)			X (day 27, 28)
Neurohormonal measurements *		X			X
Adverse experiences/concomitant meds		X	X	X	X

*PRA, angiotensin II, aldosterone

Criteria for Discontinuation from Trial:

1) When the patient decides that it is in his/her best interest.
2) When the investigator considers it advisable.
3) Intolerable adverse experiences.
4) Lack of therapeutic response resulting in intolerable symptoms.
5) Major protocol violation.
6) Noncompliance of the patient.
7) Deterioration in NYHA class starting at Visit 1 and throughout the trial.
8) Persistent SBP < 70 mm Hg after randomization and throughout the trial.
9) Persistent DBP < 50 mm Hg after randomization and throughout the trial.
10) Development of hypokalemia (< 3 mmol/l) or hyperkalemia (> 5.5 mmol/l) refractory to treatment.
11) Deterioration of renal function: > 40% change from baseline in serum creatinine.
12) Persistent PCWP < 5 mm Hg.
13) Development of any exclusion criteria (see Above).
14) Development of an arrhythmia requiring cardioversion, AICD or pharmacologic therapy during the course of the trial.

Primary Efficacy Variable :
The primary efficacy variable was the change from baseline in pulmonary capillary wedge pressure (PCWP).

Secondary Efficacy Variables:
Change from baseline to endpoint in the following:

1. Cardiac output (CO).
2. Right atrial pressure (RAP).
3. Cardiac Index (CI).
4. Systemic vascular resistance (SVR).
5. Pulmonary vascular resistance (PVR).
6. Stroke volume index (SVI).
7. Mean pulmonary artery pressure (MPAP).
8. Systolic pulmonary artery pressure (SPAP).
9. Diastolic pulmonary artery pressure (DPAP).
10. Heart rate.
11. Systolic (systemic) BP.
12. Diastolic (systemic) BP.
13. Mean arterial BP (MAP).
14. Plasma renin activity.
15. Angiotensin II.
16. Aldosterone

CO was determined by taking 5 measurements, excluding highest and lowest values, and averaging the remaining 3 values.
CI, MAP, SVR, SVI, and PVR were calculated from formulas that were prespecified in the protocol.

Sample size: The sample size was based on time available for patient enrollment. Twenty to 24 completed patients in each valsartan group and placebo, with 10-12 completed patients in the lisinopril group, were targeted for statistical analysis. A treatment difference of at least 6 mm Hg

for PCWP was considered by the sponsor to be clinically relevant. Given a standard deviation of 6 mm, and an overall significance level of 0.05 (with 0.017 significance for pair-wise treatment comparison), a treatment difference in PCWP of 6 mm Hg was expected to have a statistical power of 82.4%.

Data set analysis: According to the protocol, all randomized patients with a baseline and at least one non-missing post-randomization measurement for a particular variable were to be included in the analysis of that variable. The safety analysis was prespecified to include all randomized patients.

Although not prespecified in the protocol or amendment, three patients (one each in valsartan 40 BID, 80 BID and placebo) were excluded from the efficacy analysis population because of the use of excluded concomitant medications. These three patients were discontinued from the study and did not undergo Day 28 hemodynamic measurements. According to the sponsor, these patients were excluded prior to database lock. The patients analyzed are referred to as the "efficacy analysis population."

Statistical Plan:
The primary analyses was mean change from baseline (Day 0 Hour 0) in PCWP over 4 to 8 hours on Day 28 and at 12 hours on Day 28.

For the PCWP and other right heart pressures between-treatment analyses of change from baseline were to be performed at each individual time point at which data were collected. In addition, change from baseline over 4, 6, and 8 hours and mean change from baseline over 0 to 12 hours were to be performed. The mean change from baseline over 4 to 8 hours was expected to provide information about peak drug effect.

Mean change from baseline over 4, 6, and 8 hours was to be calculated using equal weights for each time point, based on the equal time intervals between measurements. Mean change from baseline over 0 to 12 hours was to be calculated from weights based on the trapezoidal-rule principle and the unequal time intervals between measurements; weighting was prespecified in the protocol.

Summary statistics only were to be provided for the secondary variables related to changes in pulmonary and systemic blood pressures and heart rate.

Between-treatment comparisons were based on a null hypothesis of no treatment difference. All tests were based on two-sided alternative hypotheses. Testing for between-treatment differences were made at a 5% overall significance level, using Bonferroni adjustments for valsartan 160 mg BID vs. placebo, valsartan 80 mg BID vs. placebo, and valsartan 40 mg BID vs. placebo; each individual pair-wise comparison was to be tested at the 1.7% (5% divided by 3) significance level. Lisinopril 10 mg was to be compared to placebo at the 5% significance level.

A two-way analysis of covariance was to be performed on change from baseline; the baseline value was to be used as the covariate and treatment and center were to be used as factors. This model was also to include all two-way interactions with treatment.

Safety Variables:
Monitoring of adverse experiences, clinical laboratory evaluations, vital signs and body weight.

Amendment to the Protocol:
3. (signed, April 27, 1995):
    A) PCWP inclusion criterion lowered to patients with mean PCWP $\geq$ 15 mm Hg at rest on Visit 2 (day –1);
    B) Exclusion criterion for acute pulmonary edema or hospital admission for CHF changed from "within 3 months prior to Visit 1" to "within one month prior to Visit 1."
    C) In case of premature discontinuation, all procedures and CRF pages should be completed as appropriate. Right heart catheterization should only be performed at the final visit if this visit is at least two weeks after visit 2 (day 0).
    D) If PCWP was unable to be measured at some timepoint, then the pulmonary artery diastolic pressure (PAD) was to be taken instead if the PCWP and PAD have been the same during previous measurements and the field for mean PAP in the CRF will be empty.
    E) The unit in the CRF for angiotensin II was to be changed from pmol/ml to pmol/L.
    F) In addition to PRA, angiotensin II and aldosterone, norepinephrine concentrations were to be determined at visits 2 and 5 at baseline, and at 2, 4, 8 and 12 hours post-dosing.

Neurohormone analysis:
- PRA, angiotensin II and aldosterone were to be analyzed at the laboratory of Moscow Medical Academy, B. Pirogovskaya 6, Moscow 119435.
- Plasma norepinephrine was to be analyzed by Hazleton, Otely Road, Harrogate, North Yorkshire HG31PY, England.

Batch and formulation numbers follow (Table 103.2):

Table 103.2 . Drug Supply

Treatment group	Batch Number	Formulation Number
Valsartan 40 mg	1051/6	F.1
Valsartan 80 mg	1052/6	F.1
Valsartan 160 mg	1059/4	F.1
Lisinopril 5 mg	1126/1	F.1
Lisinopril 10 mg	1127/1	F.1
Placebo	1070/13	F.1

Source: Sponsor: Volume 65 (Study report)

Administrative Issues:
1. According to the sponsor, it was noted that "a few patients had PCWP > MPAP at certain time points." Since the prespecified formula for PVR used the calculation of (MPAP-PCWP)/CO, PVR was instead calculated using the formula Total PVR = MPAP/CO.
2. For results of norepinephrine levels, 2 of 3 batches could not be analyzed because 90% of the samples were below the lower limit of detection. The third batch was discarded without being analyzed.

3. According to the Moscow Medical Academy, four neurohormonal samples for three patients (Patient 1028/22, visit 2; patient 1029/23, visit 2; patient 1075/57, visits 2 and 5) were "unreliable" and therefore excluded from analysis.
4. All calcium values from laboratory #2 measured before 10/1/95, from laboratory #4 before 11/23/95, and all values from laboratory #6 were excluded from laboratory data analysis because ionized calcium was measured instead of total calcium.

Medical Reviewer's Comments:

1) This study did not require documentation, via echocardiogram or MUGA, of extent and type of LV dysfunction.
2) It is unclear why the lisinopril doses (5/10 mg) were chosen. The effective dose range for CHF is from 5 to 40 mg once daily.[4] Patients on lisinopril may have been receiving suboptimal therapy.
3) Patients were not allowed to receive ACE inhibitors 6 months prior to Visit 1 and throughout the trial. During the period when this study was conducted, ACE inhibitors were part of standard US therapy for the treatment of CHF. Indeed, captopril was approved in the early 1980s for hypertension and was in common use, by the mid-1980s, for CHF. Captopril was apparently available in Russia as well; one patient (7/ Rand. #28) was discontinued because he was taking captopril for CHF (Source: Table 6.1-2: Premature Discontinuations).

Results:

Patient Disposition:

One hundred forty-five patients were enrolled at Visit 1; a total of 116 patients were randomized at Visit 2 and 103 patients completed the study.

Table 103.3. Patient disposition

	Valsartan			Lisinopril	Placebo	Total
	40 mgBID	80 mg BID	160 mg BID	5/10 mg		
Enrolled						145
Randomized	24*	24*	27	15	26*	116
Completed	20	21	24	14	24	103
Discontinuations from Double-Blind						
Adverse Event	1	--	1			2
Withdrew consent	1**	--	1	1	1	4
Lack of Therapeutic Effect		1***				1
Did not meet Protocol criteria	1	2			1	4
Administrative	1		1			2

*One patient in each of these groups did not have a valid hemodynamic measurement for at least one time point.
Source: Volume 65: Table 6.1-1
**This patient underwent heart transplantation; consent was withdrawn because a donor was found.
***Deterioration of CHF

[4] Source: Zestril labeling.

Protocol violations:
There were a total of 6, 8, 2 and 9 protocol violations noted in the valsartan 40 BID, 80 BID, 160 BID and placebo groups, respectively; no protocol violations were seen in the lisinopril group. As noted above, 3 patients were excluded from the efficacy analysis because of the use of excluded medications.

Drug Exposure:

Table 103.4. Duration of Drug Exposure (All Randomized Patients)

	Placebo	Valsartan			Lisinopril
		40 mg BID	80 mg BID	160 mg BID	5/10 mg
N	26	24	24	27	15
Median (days)	28	28	28	28	28
Range (days)	16-32	8-35	10-31	13-29	27-29

Source: Volume 65: Table 6.4-1

Baseline characteristics:
The randomized study population was 100% Caucasian. Mean age was 53-59 (±9-14) years. Most patients had a baseline abnormal CXR; except for 2 patients with a normal ECG, most patients had ECGs that were "abnormal but compatible." Mean heights and weights were about 168-173 (±7-8) cm and 79-85 (± 15-18) kg, respectively Mean sitting pulse rate was about 77-82 (± 9-13) bpm. Mean baseline SBP was 121-134 (± 15-20) mm Hg, mean DBP was 78-85 (± 9-11) mm Hg; baseline mean PCWP was about 20-21 (± 6-10) mm Hg and mean CO was 4.84-4.97 (±1.4-1.8) L/min. There is a higher percentage of elderly in the 40 BID group, and longer mean duration of CHF in the 160 BID group.

Table 103.5. Selected baseline characteristics

	Placebo N=26 n (%)	Valsartan			Lisinopril 5/10 mg N=15 n (%)
		40 BID N=24 n (%)	80 BID N=24 n (%)	160 BID N=27 n (%)	
Male (%)	23(89)	18 (75)	23 (96)	22(82)	10 (67)
Age ≥ 65	5 (19)	9 (38)	4 (17)	5 (22)	5 (33)
Mean duration CHF (yrs)	2.8(2)	2.6(3)	1.9 (2)	4.1(5)	2.1 (2)
Etiology*: Ischemic	16 (62)	18 (75)	20 (83)	26 (96)	11 (73)
Idiopathic	11 (42)	7 (29)	2 (8)	2 (7)	3 (20)
Hypertensive	9 (35)	10 (42)	6 (25)	11 (41)	5 (33)
Other	0	0	1 (4)	0	0

Source: Volume 65:Tables 7.1-1, 7.1-2, 7.1-3 *Note: these numbers do not add up to the total N.

Table 103.6. Visit 2 NYHA Class (Efficacy analysis population)

NYHA Class	Placebo N=25	Valsartan			Lisinopril 5/10 mg N=15
		40 BID N=23	80 BID N=23	160 BID N=27	
II	8	11	12	13	6
III	12	10	8	11	6
IV	5	2	3	3	3

Source: Volume 66: Table 8.18-1

Table 103.7. Baseline mean (±SD) neurohormone levels (Visit 2, Day 0) (Efficacy analysis population)

	Placebo	Val 40 BID	Val 80 BID	Val 160 BID	Lisinopril 5/10
N	24	19	21	24	14
Angiotensin II (pmol/ml)	11.8 (19.9)	19.2 (40.7)	6.5 (5.3)	12.8 (33.0)	7.2 (5.4)
Aldosterone (ng/ml)	27.4 (33.5)*	23.1 (22.0)	13.9 (8.1)	13.7 (8.9)	20.1 (16.8)
PRA (ng/ml/h)	1.6 (3.1)	1.4 (2.5)	0.7 (0.8)	2.2 (7.1)	1.6 (2.1)

*N=22 for this group.

Source: Volume 65: Table 8.15-1 and Volume 66: Table 8.16-1, 8.17-1

Concomitant Medications:

About 53-71% of patients were taking concomitant digoxin at trial entry. About 22-29% were on Dyazide, and about 83-93% were on furosemide. Of the beta blockers, propranolol use is listed in Table 103.8; 0-1 patients per treatment group were on atenolol. Three to four patients per treatment group were on concomitant amiodarone. The most common concomitant analgesic was aspirin; only two patients (in valsartan 160 BID and lisinopril group, respectively) were on indomethacin.

Table 103.8. Selected Concomitant Medications at Trial Entry

	Placebo N=26 n (%)	Valsartan			Lisinopril 5/10 mg N=15 n (%)
		40 BID N=24 n (%)	80 BID N=24 n (%)	160 BID N=27 n (%)	
Digitalis *	19	17	13	17	8
Furosemide	22	20	22	23	14
Digitalis *	19	17	13	17	8
Acetylsalicylic Acid	12	13	12	13	5
Propranolol**	4	4	2	2	0

*This category combines digitalis and digoxin

**This category combines propranolol and propranolol hydrochloride

Pooling: Although not prespecified in the protocol or amendment, centers were pooled such that each center and pooled center were to have at least 2 randomized, evaluable patients per treatment group in the primary analyses. Two centers had sufficient patients per treatment group; the other 7 centers were merged into one.

Efficacy—Primary efficacy variable:

Figure 103.0-2. Primary Efficacy Analysis: Change from baseline in mean PCWP
(Source: Volume 65: Table 8.1-2, Exhibit 8.1)

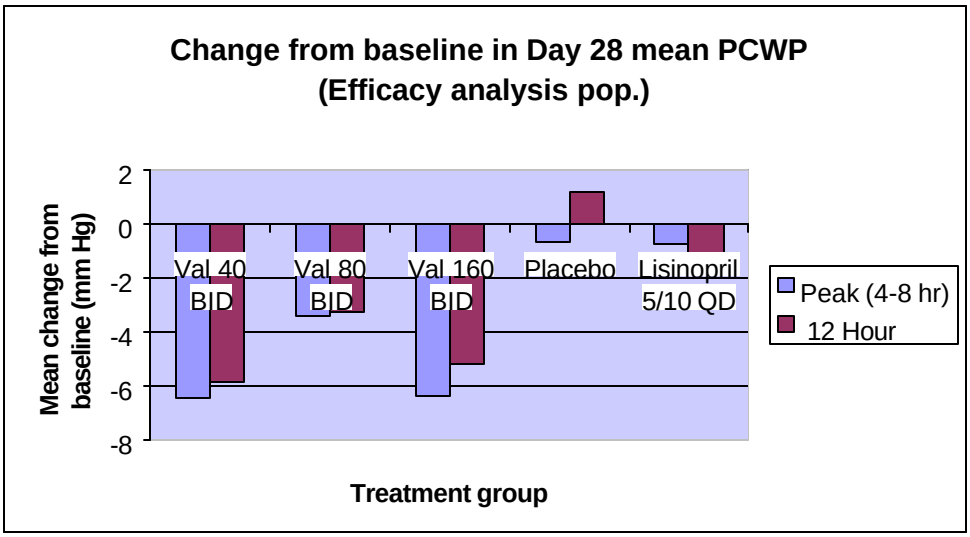


Table 103.9. Statistical Analysis Results : Day 28: Primary Efficacy Analysis (Efficacy Analysis Population)

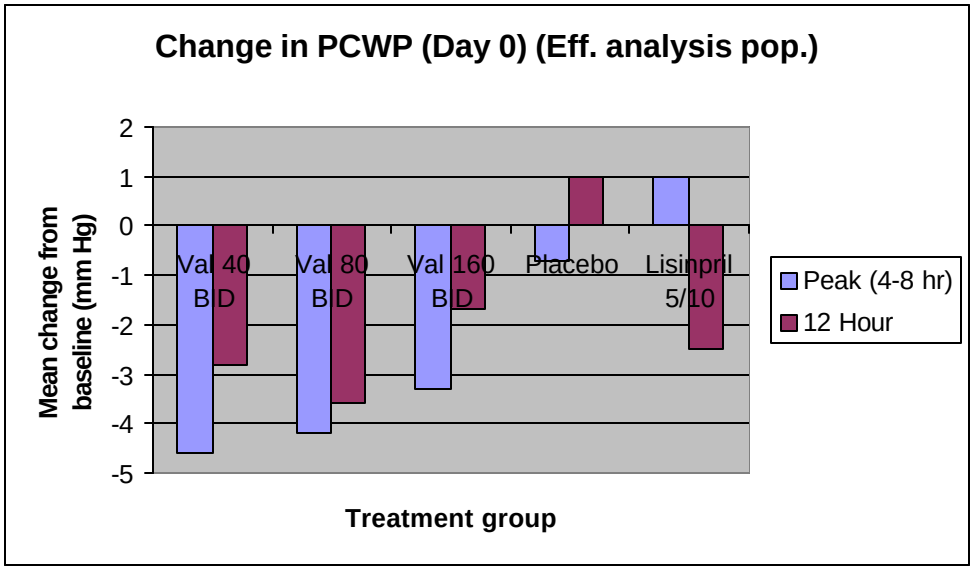
	Peak (4-8 hours after dosing)			Twelve hours after dosing		
	Adjusted mean difference	CI*	p-value	Adjusted mean difference	CI*	p-value
Valsartan 40 mg BID vs. placebo	-6.0	(-11.3, -0.7)	0.007	-7.5	(-13.2, -1.8)	0.002
Valsartan 80 mg vs. placebo	-2.8	(-7.9, 2.4)	0.194	-4.5	(-10.1, 1.1)	0.055
Valsartan 160 mg vs. placebo	-6.9	(-11.8, -1.9)	0.001	-7.5	(-12.8, -2.1)	0.001
Lisinopril 5/10 QD vs. placebo	-2.4	(-7.6, 2.7)	0.352	-5.2	(-10.8, 0.4)	0.071

Source: Volume 65: Study Report, Exhibit 8.1.2
*Confidence Interval=98.3% for valsartan; 95% for lisinopril.
**ANCOVA for change from baseline in mean PCWP. According to the sponsor, no significant treatment-by-baseline or treatment-by-center interactions were observed at either time point.

On Day 0, a dose-response can be seen for valsartan at the 4-8 hour post-dosing time point. The results for valsartan 80 mg BID at Day 28 appear inconsistent with the other valsartan results.

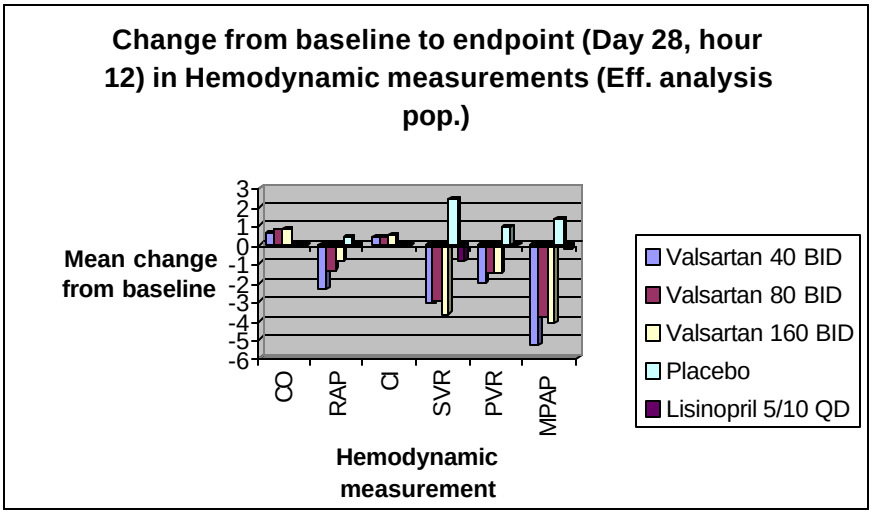
Figure 103-03. Change from baseline in Mean PCWP (Day 0)

Source: Volume 65: Table 8.1-2



Secondary efficacy variables:

Figure 103-04. Selected secondary efficacy variables (Efficacy analysis population). Raw means are presented



Source: Volume 65: Exhibit 8.2.1, 8.3.1, 8.4.1, 8.5.1, 8.6.1, 8.8.1.

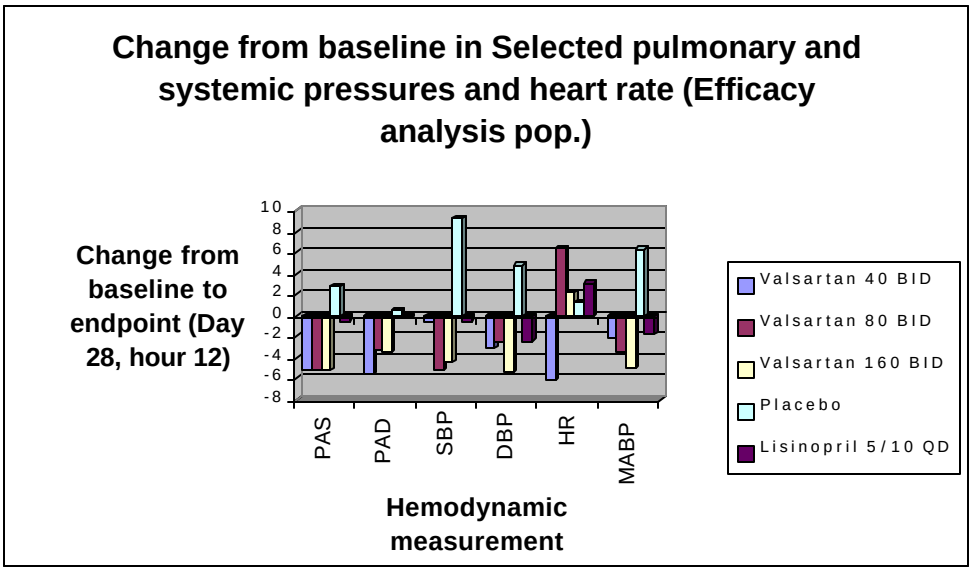
Table 103.10. Statistical analysis of secondary variables (day 28, Visit 5) (Efficacy analysis population): Change from baseline to Endpoint (12 hours post-dose) vs. placebo

	Valsartan			Lisinopril 5/10
	40 mg BID	80 mg BID	160 mg BID	
CO (L/min)				
Adjusted mean difference	0.76	1.04	1.09	0.33
Confidence Interval	(-0.12, 1.64)	(0.16, 1.91)*	(0.25, 1.92)*	(-0.47, 1.13)
RAP (mm Hg)				
Adjusted mean difference	-3.0	-1.9	-1.7	-1.0
Confidence Interval	(-6.1, 0.1)	(-5.0, 1.3)	(-4.6, 1.2)	(-3.8, 1.8)
CI (L/min/m^2)				
Adjusted mean difference	0.78	1.09	1.09	0.57
Confidence Interval	(-0.03, 0.95)	(0.05, 1.02)*	(0.20, 1.12)*	(-0.30, 0.60)
SVR (mm Hg/L/min)				
Adjusted mean difference	-5.3	-6.2	-6.2	-4.4
Confidence Interval	(-9.5, -1.0)*	(-10.4, -2.1)*	(-10.1, -2.2)*	(-8.2, -0.6)*
PVR (mm Hg/L/min)				
Adjusted mean difference	-3.11	-2.55	-2.83	-2.75
Confidence Interval	(-5.25, -0.96)*	(-4.65, -0.45)*	(-4.87, -0.78)*	(-4.87, -0.64)*
SVI (L/m^2)				
Adjusted mean difference	0.008	0.004	0.008	0.003
Confidence Interval	(0.001, 0.015)*	(-0.003, 0.011)	(0.001, 0.014)*	(-0.003, 0.010)
MPAP (mm Hg)				
Adjusted mean difference	-6.9	-4.6	-5.5	-4.9
Confidence Interval	(-12.3, -1.6)*	(-9.9, 0.7)	(-10.6, -0.4)*	(-10.8, 1.0)

Results for LS Means were, for the most part, similar to the above means and are not presented here.
Confidence Intervals =98.3% for valsartan, 95% for lisinopril. Adjusted mean difference derived from the analysis of covariance for change from baseline. Source: Volume 65: Exhibits 8.2.2, 8.3.2, 8.4.2, 8.5.2, 8.6.2, 8.7.2 *=Statistically significant

At the prespecified endpoint (Day 28, hour 12), significant increases in CO, CI and SVI and significant decreases in MPAP, SVR and PVR are seen in the valsartan 160 mg BID group compared to placebo. In all active treatment groups, RAP decreased without a dose-response or statistical significance. Results of decreases in DBP, MABP, SVR appear to show a dose-response relationship for valsartan.

Figure 103-5. Selected secondary efficacy parameters (efficacy analysis population)



Source: Volume 65: Exhibit 8.15.1, 8.16.1, 8.17.1

Neurohormone results:

Source: Volume 65: Exhibit 8.15.1, 8.16.1, 8.17.1

Figure 103-6. Neurohormone results (efficacy analysis pop.)

Source: Volume 65: Exhibit 8.9.1, 8.10.1, 8.11.1, 8.12.1, 8.13.1, 8.14.1

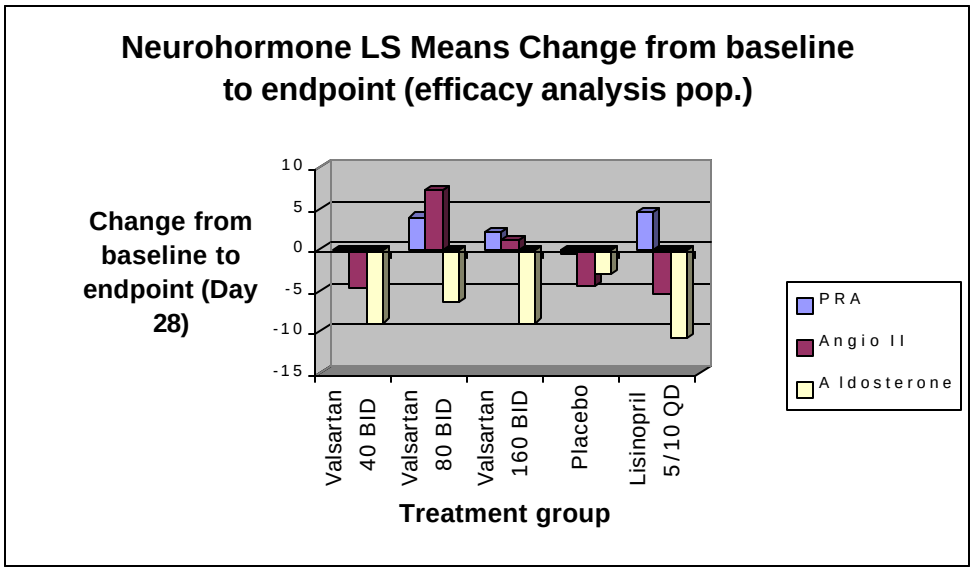


Table 103.11. Statistical Analysis of Neurohormone results (Efficacy analysis pop.): change from baseline to endpoint, Day 28, post-dose hour 12

	Valsartan 40	Valsartan 80	Valsartan 160	Lisinopril 5/10

	BID vs. placebo	mg BID vs. placebo	mg BID vs. placebo	mg QD vs. placebo
PRA (ng/ml/h)				
Adjusted mean difference	0.5	4.5	2.6	5.1
Confidence Interval	(-3.5, 4.6)	(-1.0, 10.0)	(-1.2, 6.5)	(1.4, 8.7)*
Angiotensin II ¶(pmol/ml)				
Adjusted mean difference	-0.4	11.6	5.5	-1.0
Confidence Interval	(-9.8, 9.0)	(0.1, 23.1)*	(-3.2, 14.2)	(-11.9, 10.0)
Aldosterone (ng/dl)				
Adjusted mean difference	-6.0	-3.5	-6.0	-7.9
Confidence Interval	(-12.8, 0.8)	(-10.7, 3.7)	(-13.2, 1.2)	(-13.8, -1.9)*

Adjusted mean differences were derived from the analysis of covariance for change from baseline in the selected measurements.
Confidence Intervals=98.3% for valsartan, 95% for lisinopril
¶ A statistically significant treatment-by-baseline interaction was seen at 12 hours.
*Statistically significant result

Neurohormone results are presented above. PRA appears to increase and aldosterone levels decrease in all active treatment groups compared to placebo; angiotensin II levels appear to increase in the valsartan 80 mg and 160 mg BID group. These results do not seem inconsistent with the known mechanism of action (i.e., angiotensin II-antagonism and converting enzyme inhibition) of these drugs. The results for the valsartan 40 BID group appear inconsistent with the rest of the results; however, the baseline angiotensin II value was highest in this treatment group.

Other Results:

Table 103.12. Change from baseline to final visit in NYHA Class (Efficacy analysis population-LOCF)

	Val 40 BID	Val 80 BID	Val 160 BID	Placebo	Lisinopril 5/10 QD
Worse	0	0	0	0	0
Same	13	16	15	15	7
Improved	10	7	12	10	8
Missing	0	0	0	0	0

Source: Volume 65: Exhibit 8.18.1

Results of the change from baseline in NYHA Class , as noted by the sponsor, are shown in Table 103.12. No patient, including those on placebo, was noted to worsen; however, one patient (valsartan group) was discontinued because of worsening CHF.

Mean weights did not increase or decrease by more than 1.4 kg (maximum decrease noted) from baseline to Visit 5

Safety

There were no deaths during the double-blind treatment period. Two patients (1011/85, valsartan 160 mg BID; and 1126/109, placebo) died 8 and 28 days, respectively, after trial completion . No patients were discontinued from the trial due to a laboratory abnormality.

Table 103.13. Number of Patients with Adverse Experience (occurring in more than one patient in any valsartan group)

	Val 40 BID N=24	Val 80 BID N=24	Val 160 BID N=27	Placebo N=26	Lisinopril 5/10 N=15
Total patients with adverse experiences	11	9	15	8	9
Angina pectoris	1	1	8	1	1
Cardiac Failure	0	2	1	1	0
Viral infection	2	2	4	1	0
Dizziness	4	1	2	0	1

Source: Volume 66: Table 9.1-3
Patients with multiple occurrences of the same event are counted only once in each category.

Table 103.14. Serious Adverse Experiences (including deaths)

Patient #/Center	Age	Gender	Treatment	AE	Onset (post-randomization)	Outcome
1011/84/4	48	Male	Val 160 BID	Sudden death	8 days after final visit	Died*
1017/10/4	66	Male	Val 80 BID	Angina; acute deterioration of CHF	Day 28	Recovered
1035/74/5	55	Male	Val 80 BID	Orthostatic hypotension	Day 1	Unchanged; not prematurely discontinued
1053/41/4	49	Male	Val 160 BID	Angina; sympt. VT	Day 7	Discontinued; recovered
1076/58/10	39	Male	Val 40 BID	Heart tranplantation	Day 24	Recovered
1125/96/4	68	Male	Val 40 BID	CVA	Day 10	Recovered with sequelae
1126/109/4	55	Male	Placebo	Sudden death	22 days after terminating trial	Died*

*These patients were taking ACE inhibitors after terminating the trial.

For further discussion, including evaluation of laboratory results, please see the Integrated Summary of Safety.

Medical Reviewer Comments:

1. This was a 4-week, 116 patient study of valsartan 40-160 BID, placebo and lisinopril. The efficacy parameters of this study including hemodynamic and neurohormone measurements.
2. The study design prespecified that these CHF patients were not allowed to take an ACE inhibitor for 6 months prior to the trial. As ACE inhibitors were part of standard CHF therapy, this reviewer is compelled to question whether this study design placed patients in a situation of receiving suboptimal therapy. From documentation supplied by the sponsor, 9 local IRBs (based in Moscow) approved this trial. The makeup of these IRBs and mechanism for study approval is not clear. According to an English translation of the Informed Consent, "listed" alternatives available for the treatment of chronic heart failure are hydralazine and minoxidil. Compensation is not mentioned. Consequently, the ethics of this

trial should be questioned and this reviewer will not entertain the results of this study in decisions involving valsartan.

3. Patients on lisinopril may have been on suboptimal doses. Therefore, no fair comparison can be made between lisinopril and valsartan in this trial.
4. At the highest dose of valsartan (160 mg BID), after 4 weeks of therapy, significant decreases in PCWP, compared to placebo, were seen at peak (4-8 hours post-dosing) and at 12 hours post-dose.
5. Primary efficacy variable results for valsartan 80 mg BID, at 4 weeks post-dosing, were inconsistent with the results of valsartan 40 mg BID and 160 mg BID.
6. Secondary efficacy parameters: results of the other hemodynamic variables showed a significant lowering of PVR, SVR, MPAP, nonsignificant decrease in RAP, and significant increase in CO, CI, and SVI in the valsartan 160 mg BID group compared to placebo.
7. Neurohormonal results appear to be consistent with expected drug effects.

Study 104: A Double-Blind, Placebo-Controlled, Dose Response Trial to Determine the Acute and Chronic Central Hemodynamic Effects of Valsartan in Patients with Symptomatic Congestive Heart Failure. (Phase II) (Dec. 5, 1994)

Source: NDA 20-665, S-016: Volumes 14-17; electronic datasets;

Primary Objective: Evaluate the acute and chronic central hemodynamic effects of valsartan 80 mg bid and 160 mg bid compared to placebo in patients with chronic stable congestive heart failure (New York Heart Association [NYHA] state II-IV) receiving therapeutic doses of an ACE inhibitor.

Secondary Objective: Evaluate safety and tolerability of valsartan administered to patients with chronic stable congestive heart failure (NYHA II-IV) receiving therapeutic doses of an ACE inhibitor.

Sites: 17 centers in the United States.

Duration: March 6, 1995 (first patient in) to June 8, 1996 (last patient out).

Study design: This was a 6 week, multicenter, randomized, double-blind, parallel-group as shown in Figure 104. 1.

Figure 104.1. Study Design

Period		**Single-Blind Placebo Run-in**		**Double-Blind Treatment**
				Randomization ⇓
	Visit	1	2	3.0 3.1 4 5 6.0 6.1
	Day	-14	-1	0 1 14 27 28 29
Treatment		Placebo		Valsartan 80 mg BID
				Valsartan 160 mg BID
				Placebo

At randomization, patients were stratified based on the dose of background ACE inhibitor (i.e., predefined high or low dose). As noted in Table 1, patients underwent right heart catheterization at Visits 2 and 5. Hemodynamic measurements were taken at Visits 3 (Day 0) and 6 (Day 28) at 0.5, 1, 2, 3, 4, 6, 8, and 12 hours after dosing; neurohormone measurements were also taken at Visits 3 and 6 at 0, 6 and 12 hours after dosing. During Visits 3 and 6, the patients' usual diuretic and ACE inhibitor were withheld until after the 12-hour measurement period. A single, open-label dose of lisinopril was given following each 0-hour hemodynamic measurement, replacing the patient's background ACE inhibitor; the dose of lisinopril was determined by the dose of chronic ACE inhibitor therapy (i.e., patients on low dose ACE inhibitor were given a single dose of lisinopril 10 mg; those on high dose ACE inhibitor were given a single dose of lisinopril 20 mg—per Table 104.1).

Stratification: Patients were stratified based on their Visit 2 dose of ACE inhibitor.

Table 104.1. Stratification chart

ACE inhibitor	Low Dose (total daily dose)	High dose (total daily dose)

Enalapril	≤ 10 mg	> 10 mg
Lisinopril	≤ 10 mg	> 10 mg
Captopril	≤ 75 mg	> 75 mg
Quinapril	≤ 20 mg	> 20 mg

Sample Size : The sample size used was based on time available for patient enrollment. Twenty-five completed patients per arm were to be available for statistical analysis; an estimated 15-18 sites were expected to each provide approximately 6 completed patients. A PCWP treatment difference of at least 3 mm Hg was considered to be clinically relevant. The Bonferroni multiple-comparisons procedure was used to control the family-wise error rate corresponding to the 2 pair-wise between-treatment comparisons of valsartan 80 and 160 mg bid versus placebo.

Inclusion criteria[5]:	**Exclusion criteria:**
• Males or females 18-80 years at Visit 1. Females must be postmenopausal for one year, surgically sterile, or using effective contraception with negative serum pregnancy tests throughout the trial. • Symptomatic, stable CHF (NYHA Class II-IV) for at least one month prior to Visit 1 while receiving ACE inhibitor therapy. • Able to tolerate right heart catheterization. • Mean pulmonary capillary wedge pressure (PCWP) ≥ 15 mm Hg at rest at Visit 2. • Stable fixed regimen of a therapeutic dose of an ACE inhibitor for at least 4 weeks before Visit 1. If patient also takes digitalis/diuretics, these should be on fixed doses for at least 4 weeks prior to Visit 1. For the purposes of the trial minimum therapeutic doses of the four ACE inhibitors approved for the treatment of CHF are defined as follows: enalapril 2.5-10 mg BID, lisinopril 5-20 mg QD, captopril 25-100 mg TID, quinapril 5-20 mg BID. If a patient is on another ACE inhibitor, permission must be optained from the sponsor. • Provide informed consent.	• Pregnant, nursing or women of childbearing potential not using effective contraception. • History of MI, unstable angina, acute pulmonary edema, or hospitalization for decompensated CHF within 3 months prior to Visit 1. • Angina pectoris requiring more than 5 tablets/week sublingual nitroglycerin prn. • Clinically significant primary obstructive valvular dysfunction (except MR secondary to a dilated LV). • Presence/history of restrictive cardiomyopathy or constrictive pericarditis. • Life-threatening ventricular arrhythmias or episodes of symptomatic sustained VT lasting > 30 seconds at any time during the trial. • Dyspnea of non-cardiac origin within past year. • Hepatic disease: SGOT or SGPT > 2 times the upper limit of normal, past hepatic encephalopathy, esophageal varices, or portocaval shunt. • Insulin dependent diabetes. • Non-insulin dependent diabetes with poor glucose control or neuropathy. • Renal impairment: serum creatinine ≥ 1.5 times upper limit of normal or history of dialysis. • Serum potassium < 3.0 meq/l. • Uncontrolled hypertension (BP ≥ 160/100 mm Hg) or significant hypotension (BP < 80/50 mm Hg). • Stroke or transient ischemic attack within past 6 months. • Gastrointestinal disease which could interfere with drug absorption; • Significant allergies/multiple drug allergies; • Malignancy (except basal cell skin cancer) within past 5 years.

[5] Inclusion and Exclusion criteria are taken from the protocol. Please see Amendments to the Protocol for changes in these criteria.

	• History of any other severe life-threatening disease. • Drug/alcohol use within past 2 years. • Investigational drug use within 1 month prior to Visit 1. • Participation in previous valsartan trial • History of noncompliance • Directly involved in execution of this protocol. • Any condition/lab abnormality which would interfere with evaluation of efficacy/safety.

The following medications were not allowed in this trial: antihypertensive agents except diuretics and specific ACE inhibitors (enalapril, lisinopril, captopril, quinapril); vasodilators (including hydralazine and long-acting nitrates. Sublingual nitroglycerin was allowed except 6 hours prior to hemodynamic measurements); antidepressants; antiarrhythmics (except amiodarone); psychotropic drugs (except for hypnotics and mild anxiolytics); anti-inflammatory drugs (except topical steroids and aspirin up to a maximum daily dose of 325 mg daily for cardioprotection); sympathomimetic drugs (such as pseudoepedrine, phenylpropanolamine) and bronchodilators; ergot preparations, antacids in amounts greater than package labeling, and thyroid medication (unless stable maintenance replacement dose for preceding 6 months).

Table 104.2. Schedule of procedures (104)

	Single-blind placebo run-in		Double-blind treatment ⇓ Randomization					
Visit	1	2	3.0	3.1	4	5	6.0	6.1
Day	-14	-1	0	1	14	27	28	29
Complete history/physical exam	X							
Signs/symptoms CHF	X	X		X	X	X		X
Interim/Final physical exam		X		X	X	X		X
ECG	X							
Chest X-Ray	X							
Safety laboratory tests (fasting)	X		X				X	
Serum potassium		X				X		
Serum pregnancy test	X		X				X	
Neurohormone measurements			X				X	
Administer lisinopril dose			X				X	
Right heart catheterization		X				X		
12 hour hemodynamics			X				X	
Adverse experiences		X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X
Dispense trial medication	X			X	X			

Primary Efficacy Variable: Change from baseline in pulmonary capillary wedge pressure (PCWP).

Secondary Efficacy Variables:
Change from baseline in:
1. Cardiac output (CO);

2. Right atrial pressure;
3. Cardiac index (CI);
4. Systemic vascular resistance (SVR);
5. Pulmonary vascular resistance (PVR);
6. Stroke volume index;
7. Mean pulmonary artery pressure;
8. Pulmonary artery diastolic pressure;
9. Pulmonary artery systolic pressure;
10. Heart rate;
11. Systemic diastolic blood pressure;
12. Systemic systolic blood pressure;
13. Mean systemic blood pressure (MAP);
14. Plasma renin activity (PRA);
15. Plasma aldosterone;
16. Plasma angiotensin II;
17. Plasma norepinephrine;
18. Atrial peptide.

PCWP at each time point was determined as the average of two measurements.
CO was measured by thermodilution at each time point. CO was determined as the average of three measurements after excluding the highest and lowest of five measurements.
Formulas for CI, MAP, SVR, SVI and PVR were prespecified in the protocol.

Statistical analyses:
The primary analysis was the mean change from baseline (Day 0 Hour 0) in PCWP over 4-8 hours on Day 28 and at 12 hours on Day 28.
Baseline value was defined as the last available pre-dose measurement prior to randomization for that variable (ie, the Day 0 hour 0 measurement).

For the primary variable and secondary variables 1-7 as well as 14-18, between-treatment analyses of change from baseline were to be performed at each individual time point at which data were collected (for hemodynamic variables: 0.5, 1, 2, 3, 4, 6, 8, and 12 hours for Visits 3 and 6, plus 0 hours for Visit 6). . For the primary variable and secondary variables 1-7, between-treatment analyses of mean change from baseline over 4, 6 and 8 hours and mean change from baseline over 0 to 12 hours were to be performed. Mean change from baseline over 0-12 hours was to be calculated from weights based on the trapezoidal-rule principle and the unequal time intervals between measurements (as prespecified in the protocol). Within-treatment analyses were to be performed for mean change from baseline in PCWP and CO over 4 to 8 hours and at 12 hours at Visits 3 and 6.
Between-treatments analysis:
A two-way analysis of covariance was to be performed on change from baseline for each variable analysis. The model will include all two-way interactions with treatment.
For each pair-wise comparison, 97.5% confidence intervals for the corresponding between-treatment difference was to be calculated, based on results from the analysis of covariance.

Within-treatment analysis: Within-treatment analyses of change from baseline will be performed using Student's t-test.

Safety analysis:
Monitoring of adverse experiences, laboratory evaluations, vital signs and body weight.

Amendments to the Protocol:

1. Amendment #1 (signed 3/2/95): changed the following exclusion criteria: MI, unstable angina, pulmonary edema, hospitalization for decompensated CHF changed to within one month preceding Visit 1; history of malignancy (except basal cell skin cancer changed to within past two years: antiarrhythmic exclusion changed to "Antiarrhythmic drugs with a substantial effect on myocardial performance at usual doses such as calcium antagonists, beta-blockers, flecainide, and disopyramide." Concomitant antiarrhythmics such as procainamide, quinidine, amiodarone, mexilitene or tocainide were to be allowed at recommended therapeutic doses if stablilized at least one week before randomization.
2. Amendment #2 (signed 6/15/95): allowed patients to have the Swan-Ganz catheter inserted the morning of Visits 3 and 5, with PCWP measurements taken one hour after catheter insertion; directed the patient's evening dose of diuretic (if given in divided doses) be held for the evening prior to to 12-hour hemodynamic measurements unless it is not medically acceptable to do so.
3. Amendment #3 (signed 6/23/95): allowed well-controlled type I diabetics into the trial.
4. Amendment #4 (signed 2/16/96): changed antidepressant exclusion: Excluded antidepressant drugs with significant cardiovascular effects, such as MAO inhibitors and tricyclics. Selective serotonin reuptake inhibitors (e.g. fluoxetine, paroxetine, and sertraline) with the exception of venlafaxine, are allowed if the patient has been on a stable dose two months prior to Visit 1.

Other Administrative Issues:

According to the Study Report, an unplanned interim analysis for PCWP, DPAP, and systemic diastolic and systolic blood pressure provided data for 40 randomized patients, including 36 patients with Visit 3 and 6 measurements. These interim analysis results were presented, using masked treatment codes, to internal personnel at Ciba (the Sponsor) for decision-making puposes; it was noted that "results were not analyzed by or revealed to those directly involved in the conduct or final analysis of the trial prior to final data lock."

Results:

Patient Disposition:

Table 104.3 lists patient disposition. Sixty patients were not randomized due to adverse experience (7 patients), not meeting protocol criteria (38 patients), noncompliance (1 patient), withdrew consent (12 patients) and administrative problems (2 patients).

Table 104.3. Patient Disposition

	Placebo	Valsartan 80 BID	Valsartan 160 BID	Total
Enrolled	--	--	--	143
Discontinued during placebo run-in				60
Randomized	28	28	27	83
Completed double-blind	27	24	23	74
Discontinued prematurely in double-blind	1	4	4	9
For adverse experience	0	2	2	4
For death	0	1	1	2
Administrative	1	0	1	2
Lost to follow-up	0	1	0	1

Source: Volume 14: Exhibit 6.1-1; Table 6.1:1

Table 104.4. Drug Exposure (all randomized patients)

	Placebo	Valsartan 80 mg BID	Valsartan 160 mg BID
N	28	28	27
Mean (± SD) days on trial drug	31 (5)	27 (9)	27 (8)
Range (days)	28-53	1-37	2-42

Source: Volume 14: Table 6.4:1

Baseline characteristics are shown in Table 104.5. The study population was 100% male and a majority were Caucasian; the percent of Black patients was lower in the placebo group compared to valsartan groups.

Mean age was 62-65 years with a majority of elderly in the valsartan treatment groups. Mean height was 69-70 inches and mean weight was 194-201 lbs. All randomized patients were treated with an ACE inhibitor during the trial.

Table 104.5. Baseline characteristics (all randomized patients)

	Placebo (N=28) n (%)	Val 80 BID (N=28) n (%)	Val 160 BID (N=27) n (%)
Race			
Caucasian	22 (79)	17 (61)	15 (56)
Black	3 (11)	10 (36)	9 (33)
Other	3 (11)	1 (4)	3 (11)
Mean age (± SD)	62 (9)	65 (10)	65 (10)
Age range	45-80	36-81	48-82
Age ≥ 65	11 (39)	17 (61)	15 (56)
Mean CHF duration (yrs)	6 (7)	4 (3)	6 (6)
Visit 2 NYHA Class II	16 (57)	19 (68)	17 (63)
Class III	12 (43)	9 (32)	10 (37)
CHF etiology: Idiopathic	4	6	6
Ischemic	17	15	14
Hypertensive	4	6	5
Other	3	1	2
Visit 2 Previous ACEI: high	20	20	22
Low dose	8	8	5
Visit 1 Normal ECG	0/28	1/28	1/27
Visit 1 Normal CXR	2/28	0/28	2/27

Source: Volume 14: Table 7.1:1. Electronic database.

A review of Visit 1 background medications for randomized patients showed that over 75% used digoxin and furosemide. No beta blocker use was noted.

Baseline hemodynamic measurements:
Three patients in placebo, and two patients in each valsartan group had PAD, but not hour 4-8 PCWP measurements on Day 0. Three patients in placebo, 7 patients in valsartan 80 BID, and 5 patients in valsartan 160 BID were missing peak (4-8 hour) PCWP measurements on Day 28.
Baseline hemodynamic measurements are shown below (see Table).

Baseline imbalances exist between treatment groups. It appears that mean heart rates, pulmonary artery pressures (PAS and PAD), PCWP and PCWP are higher in the Valsartan 160 mg BID group compared to

the other treatment groups. In addition, baseline mean plasma norepinephrine levels and PRA are increased in the Valsartan 160 mg BID group compared to the other two treatment arms. SVR appears to be increased in the valsartan 80 BID group.
According to the sponsor, testing for treatment group baseline comparability showed a significant difference for the placebo vs. valsartan 160 mg BID group norepinephrine level ($p < 0.05$). Analysis of baseline differences in PCWP, PAD, and MPAP for valsartan 80 mg BID vs. 160 mg BID showed a trend toward significance at the p=0.07 level.

Table 104.6. Mean (± SD) Baseline Hemodynamic Measurements at Day 0, Hour 0 (All Randomized Patients) (104)

	Placebo (N=28) n (%)	Val 80 BID (N=28) n (%)	Val 160 BID (N=27) n (%)
Systemic SBP (mm Hg)	126 (21)	125 (20)	127 (22)
Systemic DBP (mm Hg)	73 (13)	75 (12)	75 (13)
MABP (mm Hg)	91 (14)	92 (13)	92 (15)
HR (bpm)	72(10)	74 (14)	77 (14)
PAS	49 (17)	47 (15)	55 (19)
PAD	22 (7)	21 (7)	25 (9)
MPAP	31 (10)	30 (10)	35 (12)
N	27	28	27
RAP	8.9 (5)	8.0 (3)	8.6 (5)
N	27	26	25
PCWP	21 (7)	20 (7)	24 (8)
N	26	27	26
CO	4.6 (1.1)	4.3 (1.1)	4.6 (1.5)
CI	2.2 (0.4)	2.1 (0.5)	2.2 (0.6)
SVI	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)
N	26	27	26
PVR	593 (316)	608 (321)	682 (370)
N	25	27	26
SVR	1504 (475)	1633 (428)	1565 (489)

Source: Table 8.1:15a, 8.1.16a, electronic database

Table 104.7. Mean (± SD) Baseline plasma neurohormones (Day 0 Hour 0)

	Placebo (N=28)	Val 80 BID (N=27)	Val 160 BID (N=27)
N	28	27	27
Plasma norepinephrine	274 (184)	321 (148)	411 (303)
ANP	330 (339)	402 (324)	406 (262)
PRA	5.3 (9.0)	5.0 (8.2)	7.2 (11.5)
N	26	26	25
Angio II by HPLC	6.8 (17.9)	5.1 (5.8)	4.5 (5.4)
N	25	22	21
Aldosterone	94 (92)	104 (125)	97 (72)

Source: Volume 15: Table 11.1:6a

Pooling of Centers: Centers with less than 3 randomized patients per treatment group were pooled; first, these centers were sorted by total number of patients per center available for

analysis; and then by center numbers previously assigned at trial initiation. Pooling was to begin with the larger centers to be pooled and progress to smaller centers.
According to the sponsor, pooling criteria and pooling algorithm were "decided prior to unblinding double-blind treatment codes." No such information on pooling can be found in Protocol or Amendments.

Primary Efficacy Variable:
All groups, including placebo, showed a statistically significant mean decrease from baseline in mean PCWP at 4-6 hours post-dosing (seen on Day 0 and 28). All groups except Valsartan 80 mg BID, Day 28, showed a statistically significant decrease from baseline at 12 hours. Valsartan 160 mg BID, Day 28, with a higher baseline mean than the other groups, showed larger, statistically significant decreases from baseline at all measured time points.
Results of the prespecified primary analysis are shown in Table 104.8. The baseline mean is higher in the valsartan 160 mg BID group with larger decreases seen. No significant decreases compared to placebo are seen. Results for LS mean change (0-12 hours) for the valsartan groups (not shown) also did not show statistically significant results compared to placebo.

Table 104.8. Primary Efficacy Variable (all randomized patients): PCWP (mm Hg) Day 28

	Placebo	Valsartan 80 mg BID	Valsartan 160 mg BID
N	25	21	22
Baseline mean	20.26	20.36	24.86
Peak (4-8 hours) LS Mean Change from baseline	-4.39	-4.34	-6.22
97.5% Confidence Interval vs. placebo	--	(-3.96, 3.86)	(-2.05, 5.71)
p-value (vs. placebo)	--	0.98	0.28
12 hours post-dose LS Mean Change from baseline	-4.14	-3.14	-5.61
97.5% Confidence Interval vs. placebo	--	(-4.85, 2.85)	(-2.36, 5.29)
p-value (vs. placebo)	--	0.55	0.38

Source: Sponsor: Volume 14, Exhibit 8.1:1a. According to the sponsor, there were no statistically significant treatment-by-baseline or treatment-by-center interactions.

Day 0 results for PCWP at similar time points are shown in Table 104.9. There is a statistically significant decrease in PCWP for valsartan 160 mg compared to placebo at 4-8 hours post-dosing as well as the mean over 12 hours post-dose. Baseline PCWP appears higher in the valsartan 160 mg BID group; according to the sponsor, there was no statistically significant treatment-by-baseline interaction.

Table 104.9. Primary Efficacy variable (all randomized patients): PCWP (mm Hg) Day 0

PCWP, Day 0	Peak (4-8 hours)			12 hours post-dose			0-12 hours		
Treatment group	N	Baseline mean	LS Mean change	N	Baseline mean	LS Mean change	N	Baseline mean	LS Mean change
Placebo	25	21	-2.77	24	21	-2.16	25	21	-2.34
Val 80 BID	25	20	-3.72	26	20	-2.96	26	20	-3.02
Val 160 BID	25	24	-5.62	24	24	-5.15	25	24	-4.73

Treatment comparison	Difference (97% CI)	P value	Difference (97% CI)	P value	Difference (97% CI)	P value
Val 80 BID vs. Placebo	0.95 (-1.7, 3.6)	0.41	0.8 (-2.4, 4.0)	0.56	0.7 (-1.6, 3.0)	0.49
Val 160 BID vs. Placebo	2.9 (0.2, 5.5)	0.015*	3.0 (-0.2, 6.2)	0.038	2.4 (0.1, 4.7)*	0.02

Source: Sponsor: Volume 14, Exhibit 8.1-1b. LS Mean= Least square mean change from baseline. According to the sponsor, there were no statistically significant treatment-by-baseline or treatment-by-center interactions.
*=statistically significant

Figure104-2. Placebo-subtracted change from baseline in PCWP by hour and treatment group (all randomized patients) (Day 28).

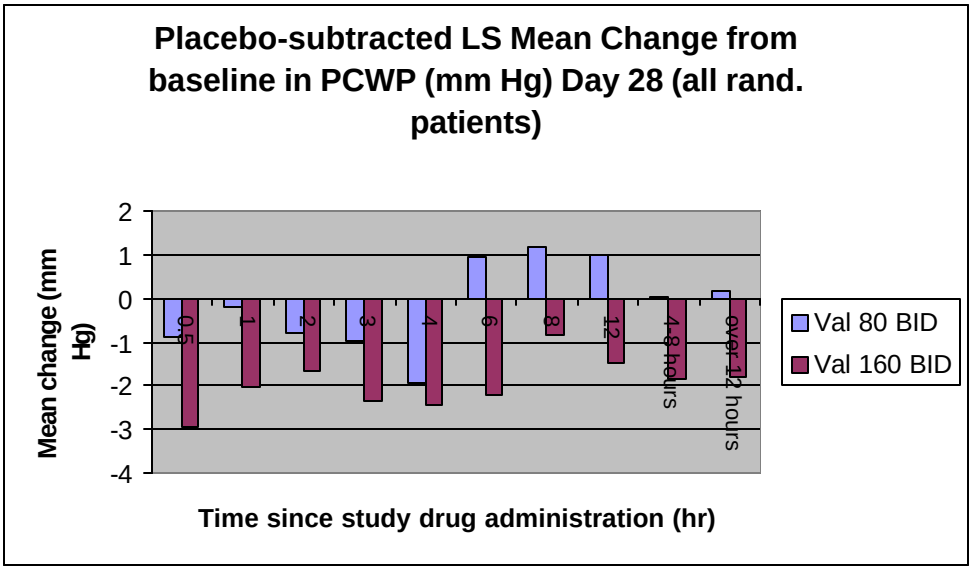
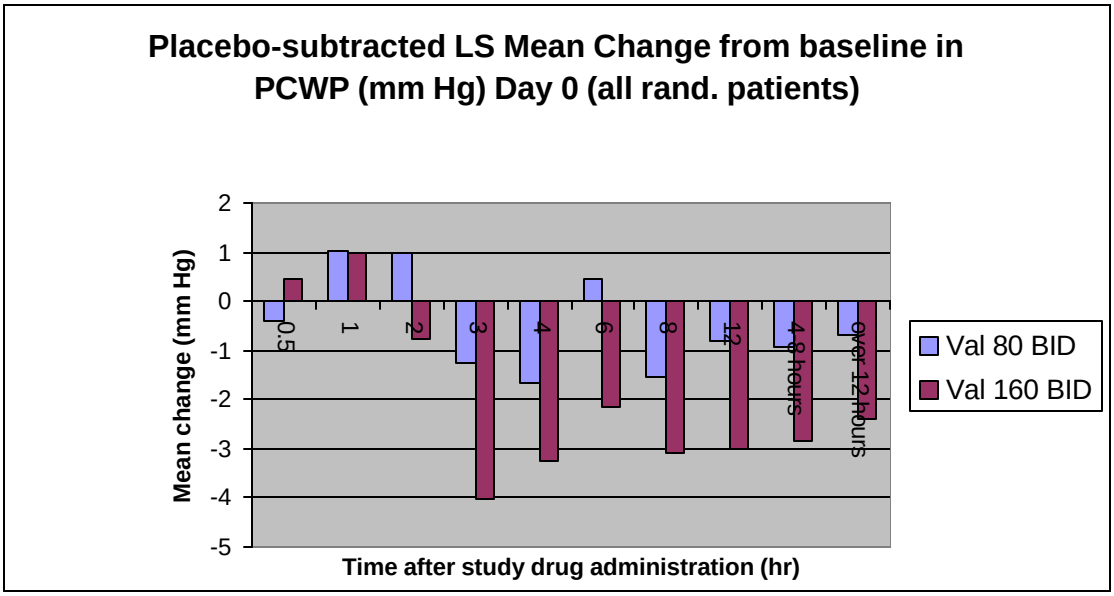


Figure 104-3. Placebo-subtracted change from baseline in PCWP by hour and treatment group (all randomized patients) (Day 0).



Source for Figures 2 and 3: Volume 14: Table 8.1:1a

Figures 104.2 and 3 show placebo-subtracted LS mean change from baseline in PCWP on Days 0 and 28. Statistically significant differences ($p < 0.025$ based on Bonferroni adjustment for 2 comparisons) were seen for valsartan 160 mg BID at 3, 4, and 8 hours, at 4-8 hours, and over 12 hours. Analysis of LS mean (placebo vs. valsartan) comparisons of changes from baseline PCWP on day 28 did not show statistically significant differences for either dose at any time point.

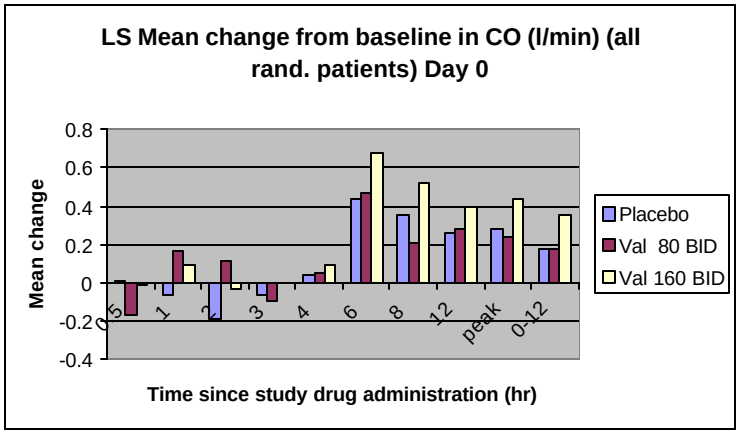
Seconday efficacy variables:

Hemodynamic measurements:

No statistically significant differences compared to placebo were noted in the analyses of CO, CI, and PVR. Significant changes from baseline were noted at 6 hours for placebo, valsartan 80 mg BID (both acute and chronic), and for valsartan 160 mg BID (Day 0 only).

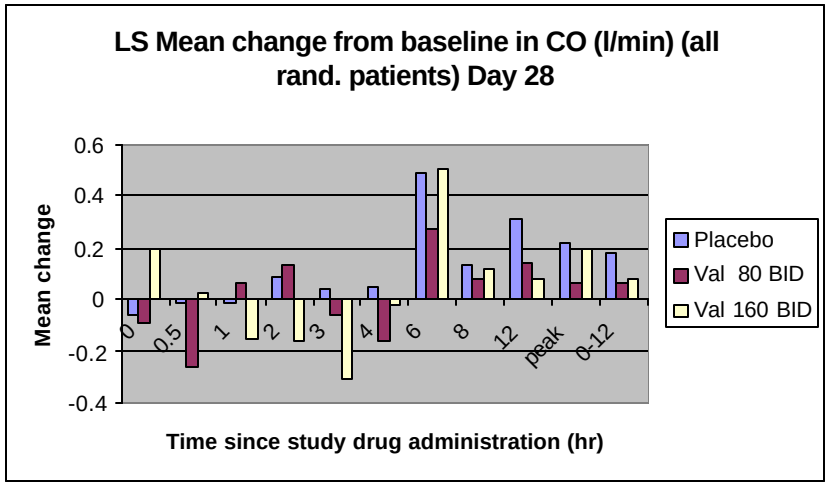
Cardiac Output:

Figure 104-4. LS Mean Change in CO (all rand. Patients) Day 0



Source for Figures 4 and 5: Volume 14: Table 8.1:2a

Figure 104-5. LS Mean change in CO (all rand. patients) Day 28



Changes from baseline in several secondary hemodynamic variable are difficult to interpret given the baseline differences between treatment groups. Therefore, they will not be presented here.

There were slight increases in heart rate in the placebo group (days 0 and 28) and slight decreases or no change in heart rate in the valsartan 160 BID group.

Neurohormone results:

Angiotensin II:: No significant differences were seen in the valsartan groups vs. placebo in the change from baseline (Visit 3, Day 0, hour 0) to selected time points on Day 0 or 28 for plasma renin activity (excluding degraded samples), angiotensin II (HPLC) (excluding degraded samples and outliers), atrial peptide, and serum norepinephrine (excluding degraded samples).

Analysis of plasma aldosterone showed significant decreases in both valsartan treatment groups compared to placebo at Day 28 (at 0, 6 and 0-12 hours). For valsartan 160 BID, significant decreases from baseline compared to placebo occurred on Day 0, 6 hours and Day 28, 12 hours as well. Given the effect of the drug, this would be an expected outcome.

Safety:

Deaths:

Patient ID	Site	Treatment	Study Day	Cause of Death
115	M0014T	Val 80 BID	Visit 4 (9/17/95)	Sudden Death at Home
158	M0019M	Val 160 BID	Visit 4 (12/5/95)	Cardiac Arrest

For further safety discussion please see the Integrated Summary of Safety.

For treatment-emergent adverse experiences please see the Integrated Summary of Safety.

Conclusions:

1. Significant decreases in PCWP were seen acutely for valsartan, compared to placebo, but not at Day 28.
2. Baseline differences between treatment groups made interpretation of results difficult.

Study 106: Multicenter, randomized, double-blind, placebo-controlled, parallel trial to assess the effect of valsartan on exercise capacity, quality of life, and signs and symptoms, in patients with stable, chronic, congestive heart failure (NYHA Class II-IV) (Phase III) (Protocol date: 12-16-96)

Source: Volumes 22 (Protocol); Volume 20 (study report); electronic datasets;

Sites: 120 centers (100 in US, 7 in South America, 13 in Canada)
Study Duration: August 18, 1997 (first patient enrolled) to May 23, 2000 (last patient completed).

Objectives:

- Compare effects of valsartan 40 mg bid, 80 mg bid, 160 mg bid and placebo, on the primary efficacy variables of exercise capacity and quality of life as well as on secondary variables including signs and symptoms of CHF, ejection fraction and NYHA class in patients with stable, chronic congestive heart failure (NYHA Class II-IV).
- Evaluate overall tolerability of each valsartan dose regimen in this patient population.

Study Design: Multicenter, randomized, double-blind, placebo-controlled, parallel trial in patients with stable, chronic congestive heart failure (NYHA class II-IV), as shown in Figure xx. Patients were randomized to one of 4 treatment groups; during the first week postrandomization, the valsartan 160 mg bid group received valsartan 80 mg bid, and then, if standing SBP $\geq$ 80 mm Hg, underwent a forced titration to the 160 mg bid dose. The other treatment groups remained on their randomized dose of medication.
Patients received standard CHF background therapy and were stratified, at randomization, according to their use of ACE inhibitors as regular medications.

Figure 106-1. Study Design (106)

Screening/ washout	Single-blind placebo run-in	Double-blind treatment

⇓ Randomization

	Placebo	Valsartan 80 mg bid	Valsartan 160 mg bid
		Valsartan 80 mg bid	Valsartan 80 mg bid
2 weeks	1-2 weeks	Valsartan 40 mg bid	Valsartan 40 mg bid
		Placebo	placebo

Visit	1	(2)	3	4	5	6	7	8
Week	-2 to –1	-1 to 0	0	1	4	8	12	16

Inclusion Criteria:[6]	**Exclusion Criteria:**

• Males and females; ≥ 18 years of age, NYHA Class II-IV CHF diagnosed at least 3 months prior to Visit 1. Females must be postmenopausal for one year, surgically sterilized or using effective forms of contraception with negative pregnancy tests throughout the trial.
• Resting ejection fraction < 35% on multiple gated acquisition radionuclide angiography (MUGA) obtained at/within one week prior to Visit 1.
• Stable doses of heart failure medications for two weeks prior to Visit 1 and during placebo run-in period.
• Ability to exercise between three and 14 minutes of a maximal exercise protocol (Modified Naughten Protocol) on each required exercise test (2-3 tests) during placebo run-in with an endpoint of fatigue or shortness of breath on each test. Two consecutive tests with a duration of exercise within 25% of each other are required for randomization.
• Provide written informed consent.
	• Pregnancy, nursing, or women of childbearing potential not practicing effective contraception.
	• Patients with:
	  • Right heart failure due to pulmonary disease;
	  • Postpartum cardiomyopathy;
	  • Hemodynamically significant mitral stenosis or regurgitation (MR) except MR secondary to LV dilatation;
	  • Hemodynamically significant obstructive lesions of LV outflow tract, including aortic stenosis and obstructive hypertrophic cardiomyopathy;
	  • Infective cardiomyopathy (Chagas' disease);
	  • Rapidly deteriorating or uncompensated heart failure;
	  • Stroke, MI or cardiac surgery including percutaneous transluminal coronary angioplasty within past 3 months;
	  • CAD likely to require CABG or PTCA;
	  • unstable angina or angina precipitated by exercise within 3 months prior to Visit 1;
	  • Hemodynamically significant or life-threatening VT occurring within 3 months prior to Visit 1 without current antiarrhythmic drug therapy;
	  • Presence or history of any additional disturbance in cardiac rhythm, rate, or conduction which would contraindicate exercise testing or would likely result in premature discontinuation of exercise for arrhythmia;
	  • Patients with pacemakers or automatic implantable cardioverter defribrillator (AICD);
	  • Peristent standing systolic BP < 100 mm Hg;
	• Uncontrolled hypertension (BP persistently above 160/100 mm Hg);
	• Poorly controlled diabetes mellitus;
	  • Serum creatinine > 2.5 mg/dl or SGOT > 3 times normal or other laboratory abnormalities indicative of serious disease other than CHF;
	  • Limited ability to exercise for any reason other than CHF;

[6] Inclusion and Exclusion criteria were taken from the Protocol. Please see Protocol Amendments for changes to these criteria during the trial.

	• Serious lung disease likely to impact exercise capacity (patients with significant chronic obstructive lung disease may not be enrolled unless the FEV1/FVC > 0.60); • History of significant psychological symptoms or illness that would impact on exercise effort, compliance or self-assessment of well-being; • Any condition that would jeopardize evaluation of efficacy or safety; • Any condition that would be a contraindication to treadmill exercise; • Contraindication to use of angiotensin II antagonists; • Prior or current participation in valsartan CHF trials; • Other investigational drugs within 30 days prior to Visit 1; • The following medications within 3 months prior to Visit 1: angiotensin II receptor antagonists, chronic intermittent intravenous inotrope or vasodilator therapy; • The following medications within 2 weeks prior to Visit 1: beta-blockers except ophthalmic preparations in stable dosage, calcium channel blockers, drugs with potent vasodilatory effects (e.g. hydralazine, prazosin, and long acting nitrates);

Exercise Testing Criteria:
In order to be eligible for randomization, patients must have had two consecutive maximal exercise tests during the run-in period, both of which were terminated for dyspnea or fatigue, with exercise times between 3 and 14 minutes and with total exercise times that did not differ by more than 25% between the two tests. These criteria may be satisfied at Visits 1 and 2 or at Visits 2 and 3. If patients fail to meet stabilization criteria at Visit 2, a subsequent Visit 3 will be scheduled. If the criteria were met at Visit 3, then double-blind Visit 3 medication were to be dispensed after exercise testing and Visit 4 was to be scheduled. If the criteria were not met at Visit 3, then the patient was to be discontinued from the study.

Titration Criteria: All patients were to be evaluated at Visit 4 to determine eligibility to continue in the trial. If the average of three standing SBP readings, obtained two minutes apart, was not $\geq$ 80 mm Hg, then the patient was to be discontinued from the study (irrespective of treatment group).

Concomitant Medication: Patients should be on a stable pharmacologic CHF regimen for at least two weeks prior to Visit 1 and during the placebo run-in period. Permitted medications included diuretics, ACE inhibitors and digoxin. Excluded concomitant medications were: 1. Angiotensin II antagonists and chronic intermittent intravenous inotrope or vasodilator therapy within 3

months prior to Visit 1 and during the trial; 2. Beta blockers, calcium channel blockers and vasodilators (such as hydralazine and long-acting nitrates) during the two weeks prior to Visit 1 and during the trial. Patients requiring these drugs after enrollment were to be discontinued from the study prior to beginning treatment with the excluded medication.

Intermittent therapy with short acting drugs with acute hemodynamic effects (e.g., sublingual nitroglycerin, parenteral or aerosolized bronchodilators, oral or nasal decongestants) was permitted but these drugs were not to be administered within 6 hours prior to any visit.

Table 106.1. Schedule of Trial Procedures (106)

Period	Screen	Single-blind placebo			Double-blind treatment				
Visit		1	(2)	3⇓	4	5	6	7	8
Week		-2 to -1	-1 to 0	0	1	4	8	12	16
Informed consent	X								
History/Physical examination		X							
Adverse Experiences			X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X
Quality of Life Questionnaires		X	X	X	X	X	X	X	X
Interim/Final physical examination			X	X	X	X	X	X	X
NYHA Class		X	X	X	X	X	X	X	X
LV Ejection fraction (MUGA)		X							X
Signs/symptoms		X	X	X	X	X	X	X	X
12-lead ECG		X[1]							
CXR		X[2]							
Safety laboratory tests*		X				X	X	X	X
Chemistry only					X				
Serum pregnancy test (women of childbearing potential only)		X	X	X	X[3]	X[3]	X	X	X
Exercise tolerance test (ETT)**		X	X	X	X	X	X	X	X
Dispense trial medication		X	X	X	X	X	X	X	X
Termination sheet									X[4]

⇓ = Randomization *hematology, chemistry, urinalysis

**ETT was performed at approximately 12 hours after the patient's previous evening dose.

[1]Baseline ECG with interpretation. Additional ECGs will be done prior to each exercise test without a formal interpretation entered into the CRF.

[2]unless obtained within past 6 months.

[3]only for patients who discontinue prematurely from the study. [4]or earlier if premature discontinuation.

Signs and symptoms review: Signs and symptoms of CHF were to be reviewed by the physician at each visit with scores (absent/present) for paroxysmal nocturnal dyspnea, dyspnea at rest, dyspnea on effort, jugular venous pressure > 10 cm above right atrium, and third heart sound; edema, fatigue, rales and orthpnea were to be scored as prespecified in the protocol.

Safety monitoring: adverse experiences, routine laboratory evaluations, vital signs and body weight.

Criteria for removal of patients from trial:

1. Patient request;
2. When investigator considers it in the patient's best interest;
3. Intolerable adverse experiences;
4. Major protocol violation;
5. Noncompliance;

6. Development of hyperkalemia (> 5 mmol/L) or hypokalemia (< 3 mmol/L) refractory to treatment;
7. Deterioration of renal function with variation of serum creatinine of 50% as compared to baseline (Visit 1);
8. Development of any of the Exclusion criteria as above;
9. Development of any contraindication to exercise testing;
10. Persistent standing SBP < 80 mm Hg;
11. Symptoms due to hypotension (syncope, faintness, orthostatic dizziness).

Primary Efficacy Variables:
1. Change from baseline in mean exercise tolerance time (ETT), using a symptom-limited exercise tolerance test; baseline ETT was that obtained at the last visit of the placebo run-in period (Visit 2 or 3);
2. Change from baseline in overall score for the Minnesota Living with Heart Failure quality-of-life questionnaire (LHFQ).

Patients were to exercise on a calibrated treadmill according to a set schedule (prespecified in the protocol) and stopped exercising when they developed fatigue and/or dyspnea compatible with exhaustion and equal to a Borg scale of perceived exertion of 17-20. Within-patient variation was to be minimized by using the same operator for all ETT, maintaining a constant level of temperature/humidity, instructing the patient to use support rails for balance only, and using maximal testing unless safety reasons mandated termination.

Secondary Variables: 1. Signs/symptoms of CHF (PND, dyspnea at rest, dyspnea on effort, fatigue, orthpnea, JVP > 10 cm above right atriaum, edema, rales, or third heart sound); 2. Change from baseline in ejection fraction; 3. NYHA Classification; 4. Change from baseline in physical scores for the LHFQ; 5. Change from baseline in emotional scores for the LHFQ;

The LHFQ was to be self-administered under a specific procedure (as prespecified in the protocol). Patients unable to comprehend the questionnaire were to be excluded from this evaluation.

Statistical Plan:
Adjustment for multiple primary endpoints:
To achieve an overall significance level ≤ 0.05, an adjustment for two primary endpoints was to be made, with each primary endpoint tested at a 2-sided significance level of 0.02532, based on the Dunn-Sidak inequality ($\alpha' = 1 - (1-\alpha)^{1/2}$, where $\alpha' = 0.02532$ when $\alpha = 0.05$).

The null hypothesis tested is that there is no treatment difference among all valsartan doses and placebo versus the alternative hypothesis that at least one of the valsartan doses has a treatment effect different from placebo.

Sample Size Calculation: The sample size was determined to detect the following treatment difference for each primary endpoint with a power of > 80% at the two-sided significance level of 0.02532 (using the Dunnett's multiple-comparisons procedure adjustment for 3 treatments versus a control): 1. For ETT, a treatment difference of 55 seconds, assuming a standard deviation of 130 seconds; 2. For overall score of the Minnesota LHFQ, a treatment difference of 10 assuming a standard deviation of 24. These standard deviations, according to the sponsor, are estimated based on available clinical trial results. The sponsor has calculated a total of 540 completed patients (135 per treatment group); to allow for a 20% premature discontinuation rate, a total of

700 patients would need to be randomized in order to reach the targeted number of 540 patients completing the study.

Data Sets Analyzed:

1. ITT (all randomized patients who had baseline and post-baseline measurements for a given efficacy variable): The primary dataset for all variables was prespecified to include all randomized patients. For the primary efficacy variable of ETT, four analysis time points will be included: Week 8, Week 12, Week 16, and terminal visit (endpoint). Imputation for missing ETT measurements was to be made because of inability to walk due to severity of CHF or because of death; a value of zero was to be used for the missing ETT measurement. Otherwise, no value substitution will be made for the missing ETT measurement. The endpoint measurement consisted of the last value carried forward after imputation for missing ETT measurements. LHFQ scores (overall, physical, and emotional) will be analyzed at each visit as well as at endpoint. Signs/symptoms of CHF and NYHA classification will be analyzed at each visit as well as endpoint. Change from baseline in ejection fraction will be analyzed at the last visit only. No imputation for missing values is planned for these secondary variables. The endpoint (terminal visit) analysis is considered primary.

2. Clinically assessable patients (CAP) (all randomized patients who took double-blind study medication,did not violate specified protocol criteria, and had baseline and post-baseline measurements for a given efficacy variable): Results from clinically assessable patients will be analyzed at the endpoint (terminal visit) for the primary efficacy variables, ETT and overall LHFQ score. These analyses will be compared with the analysis of all randomized patients; the criteria for designating patients to be "clinically assessable" was to be determined prior to database lock for analysis.

Comparisons of valsartan versus placebo were based on a null hypothesis of no treatment difference. All tests were based on two-sided alternative hypotheses. ETT and overall LHFQ were the two primary efficacy endpoints to be analyzed for this trial. To adjust for multiplicity of two primary endpoints and to achieve an overall significance level of ≤ 0.05, each primary endpoint was analyzed at a 2-sided significance level of 0.02532 based on the Dunn-Sidak inequality: $á' = 1 - (1-á)^{½}$ (where $á' = 0.02532$ when $á = 0.05$).

Treatment group comparability:
Treatment group comparability was to be examined for the following variables using the Cochran-Mantel-Haenszel (CMH) chi-square test:

- Sex, race (White, Black, Other), significant medical history/other concomitant diagnosis (yes/no), CHF etiology (ischemic/nonischemic), background ACE inhibitor therapy (yes/no), background diuretic use at baseline (yes/no), background use of digoxin at baseline (yes/no), previous hospitalization for CHF (yes/no)

Treatment group comparability for all randomized patients was to be examined using the F-test for the baseline values of the following variables:

- Age, height, weight at Visit 1, duration of CHF.

Treatment group comparability for ETT, ejection fraction, and LHFQ scores at baseline will be examined using the F-test; treatment group comparability for baseline NYHA classification and signs and symptoms of CHF will be examined using the CMH chi-square test.

Primary Analysis, primary efficacy variable (ETT):
A two-factor ANCOVA was to be performed for change from baseline in ETT, with center and treatment group as factors and baseline mean ETT value and baseline ACE category (yes/no) as covariates. It was planned that treatment-by-center, treatment-by-baseline ETT, and treatment-by-baseline ACE category interaction terms will be included in this model. Missing ETT measurements during the double-blind period, because of inability to walk due to CHF or because of death, were given a value of zero. Otherwise, no value substitution was to be made for missing ETT measurements. After substitution for missing values, the last value will be carried forward for the endpoint (terminal visit) analysis.

Supplementary Analysis, primary efficacy variable (ETT):
A nonparametric analysis of ETT ranks was to be performed for robustness purposes (RANCOVA).

Analysis of primary efficacy variable (overall score LHFQ):
A two-factor ANCOVA was to be performed, with center and treatment group as factors and baseline overall LHFQ score and baseline ACE category (yes/no) as covariates. It is planned that treatment-by-center, treatment-by-baseline LHFQ, and treatment-by-baseline ACE category interactions terms will be included in the model. If a patient is missing 25% or less of the individual component scores for overall LHFQ at a visit, then the average of the available LHFQ component scores for the patient at that visit will be used in place of the missing component scores at that visit. If more than 25% of a patient's overall LHFQ component scores are missing at a visit, then the overall LHFQ value for the patient will be considered missing at that visit. After substitution for missing values, the last value will be carried forward for the endpoint (terminal visit) analysis.

Pooling of centers: Some centers may be pooled as necessary in order to achieve an examination of treatment-by-center interaction. Pooling was to be performed so that, for analysis of ETT change from baseline, all time points will have at least 3 randomized patients per treatment group in all pooled centers. A pooling algorithm was prespecified in the protocol.

Analyses of secondary efficacy variables: ANCOVA was to be used for analysis of change from baseline in ejection fraction as well as physical and emotional LHFQ scores. No imputation for missing values was planned for ejection fraction; the imputation for LHFQ scores was to be the same as described for overall LHFQ score.
A CMH chi-square test for different treatment means, adjusted for ACE category and baseline value, was to be used for analysis of NYHA class and signs/symptoms of CHF.

Amendments to the Protocol:

1. Amendment #1 (May 15, 1997 not signed): A) Changed sample size to approx. 700 patients randomized in order to obtain the 540 required patients who meet all randomization criteria, have baseline/post-baseline data for both primary efficacy variables, and completed all visits per protocol. B) Modified ETT inclusion criteria of exercise duration based on age (18-29 years, exercise duration of 3-14 mins; 30-50 years, duration of 3-12 mins; over 50 years, duration of 3-10 mins). C) Amended exclusion criterion for chronic obstructive lung disease (ratio of FEV1/FVC > 0.60 and FVC is > 60% of predicted). D) Amended randomization assignment numbers to country-specific sequences and included stratification. E) Amended recording of concomitant therapy to include all medications, including non-drug and non-prescription therapies. F) Added recording of exercise-related AE on the CRF.

2. Amendment #2 (May 8, 1998 not signed): A) Revised enrollment and randomization numbers for centers in the US and South America. B) Changed washout period (from 2 weeks) to 1-3 weeks. C) Amended inclusion MUGA result (from < 35% within 1 week prior to Visit 1) to ≤ 40% within 2 weeks of Visit 1. D) Included as background medications vasodilators (hydralazine and long-acting nitrates), alpha-adrenergic blockers and calcium channel blockers at a stable dose beginning at least 1 week prior to the MUGA scan. E) Eliminated exclusion of pacemaker or AICD.
3. Amendment #3 (signed, November 19, 1998): A) Added "that patients should be on a stable beta-blocker dose beginning at least one week prior to the baseline qualifying MUGA through the randomization visit. " B) Removed beta-blockers from excluded medications.
4. Amendment #4 (January 24, 2000, not signed): A) Added enrollment and randomization numbers for USA; B) Changed sample size calculation to include statistical adjustment for two primary endpoints, based on the Dunn-Sidak inequality, using a 2-sided significance level of 0.02532 for each primary endpoint. For each primary endpoint, a further sample-size adjustment was made for comparing 3 valsartan doses versus placebo based on Dunnett's procedure. C) Revised methods of adjustment for multiple endpoints and multiple comparisons. Stated a joint null hypothesis consisting of the two individual null hypotheses (for each primary endpoint, respectively) with testing based on Hochberg's multiple-testing step-up procedure to ensure an overall á-level at 0.05. Planned imputation for post-baseline ETT separately for each ACE category (assigning the lowest rank to death, next lowest rank to patients unable to walk possibly due to CHF, next rank to patients unable to walk due to reasons other than possibly due to CHF, and the next rank to patients who can walk). D) Analysis of LHFQ and imputation of missing values: For patients completing all 21 individual scores, the overall score will be the sum of the corresponding 21 individual scores. A patient missing more than 25% of individual scores will have a missing overall LHFQ for that visit. If a patient is missing 25% or less of individual scores at a visit, then the average of the non-missing individual scores for the patient at that visit will be used in place of the missing individual scores at that visit. E) Analysis of the two secondary LHFQ scores will be analogous to analysis of the overall LHFQ score. F) Pooling was to be performed so that, for the change from baseline for ETT and LHFQ, all common analysis time points will have at least 3 randomized patients available per treatment group in all pooled centers.

Results:

Patient Disposition:

Nine hundred five patients were enrolled. One hundred thirty-five were discontinued during the placebo run-in period (23 for an adverse experience, 6 for an abnormal laboratory value, 2 for abnormal test procedure results, 88 because they did not meet protocol criteria, 2 for noncompliance, 10 for withdrawal of consent; 3 were lost to follow-up and 1 patient died). Of those randomized, 83-85% of patients were from the US, 8-10% from Canada, and 7-8% from Argentina. There were no meaningful differences between treatment groups.

Table 106.2. Patient Disposition

	Placebo	Valsartan 40 mg BID	Valsartan 80 mg BID	Valsartan 160 mg BID	Total
Enrolled	--	--	--	--	905
Randomized	192	185	195	198	770
Completed	169	151	167	163	650
Discontinued prematurely from double-blind	23	34	28	35	120
Adverse experience	9	22	17	20	68
Abnormal lab value	--	--	--	2	2
Unsatisfactory therapeutic effect	1	--	--	--	1
Does not meet protocol criteria	2	4	5	8	19
Noncompliance	2	2	1	1	6
Consent withdrawn	3	1	1	1	6
Lost to follow-up	1	1	3	--	5
Administrative issues	1	1	--	--	2
Death	4	3	1	3	11

Source: Table 7.1-1, 7.1-2a (Volume 20) and enroll.xpt, vpdisc.xpt

Protocol Deviations:
Of those randomized, 6% (placebo) to 12% (160 BID group) were noted to have protocol violations that led to exclusion from the Clinically Assessable analysis (see below). The major protocol violation of note, ETT duration outside required range for age category, occurred at a rate of 4-8% (8-16 patients), the highest percentage being in the valsartan 160 BID group and the lowest percentage in the placebo group. In addition, more patients in the valsartan 40 mg BID had a visit 1 standing SBP < 100 mm Hg (10.3%) than in the other groups (2.1-3.6%).

Table 106.3. Populations analyzed

	Placebo	Valsartan 40 mg BID	Valsartan 80 mg BID	Valsartan 160 mg BID
All randomized	192 (100)	185 (100)	195 (100)	198 (100)
SAP	192	185	194 (99.5)	197 (99.5)
ITT (ETT endpoint)	179 (93)	168 (91)	180 (92)	182 (92)
ITT (LHFQ endpoint)	172 (90)	166 (90)	175 (90)	177 (89)
CAP (ETT endpoint)	170 (89)	159 (86)	168 (86)	167 (84)
CAP (LHFQ)	161 (84)	156 (84)	164 (84)	161 (81)

Source: Table 7.3-1 (Volume 20).
SAP=Randomized patients who took study medication and had at least one post-baseline assessment for any safety measurement.
ITT=Randomized patients who took study medication and had baseline and at least one post-baseline efficacy measurement for a given variable. CAP=Clinically assessable population

Other Patients Excluded from Analyses:

- Two patients (#1498/0143 and 1535/0158) were assigned to valsartan 80 mg BID and 160 mg BID groups, respectively, but did not take study drug medication; therefore, both patients were excluded from the SAP and CAP populations.
- Sixty-one randomized patients were excluded from the ITT population for the primary ETT endpoint analysis: 15 of these patients were unable to walk for reasons other than CHF and the rest did not have post-randomization ETT information (either recorded or imputed).
- Eighty randomized patients were excluded from the ITT population for the primary overall LHFQ analysis, including 53 Argentinian patients who did not participate (the questionnaire was not validated in non-English speaking patients) and 27 patients who either did not participate for the same language reason or had no post-baseline measurements with $\geq$ 75% of the questions answered.
- A total of 106 and 128 randomized patients were excluded from CAP for ETT and LHFQ, respectively.

Baseline Characteristics:
The randomized population was mostly (79-83%) male and over 80% Caucasian; the valsartan 80 mg BID group appeared to have a slightly higher percentage of Caucasian and a smaller percent of Black patients. Otherwise, there appeared to be no meaningful differences between the treatment groups.

Table 106.4. Baseline Demographics (ITT)

	Placebo (N=192) n (%)	Valsartan 40 mg BID (N=185) n (%)	Valsartan 80 mg BID (N=195) n (%)	Valsartan 160 mg BID (N=198) n (%)
Gender:				
Male	154 (80)	146 (79)	161 (83)	158 (80)
Female	38 (20)	39 (21)	34 (17)	40 (20)
Race:				
Caucasian	156 (81)	156 (84)	171 (88)	159(80)
Black	25 (13)	22 (12)	18 (9)	30 (15)
Oriental	2 (1)	--	2 (1)	--
Hispanic	4 (2)	6 (3)	2 (1)	7 (4)
Other	5 (3)	1 (0.5)	2 (1)	2 (1)
Age:				
< 65	100 (52)	98 (53)	105 (54)	97 (49)
$\geq$ 65	92 (48)	87 (47)	90 (46)	101 (51)

Source: Table 7.4-1a, 7.4.1-b (Volume 20)

About 53-57% and about 42-46% of randomized patients, respectively, fell into NYHA Class II and Class III CHF; less than 3% of patients were in NYHA Class I or IV. Prior to randomization, about 63-73% of patients used background digoxin, 79-85% of patients used diuretics, 85-90% of patients used ACE inhibitors, 24-31% of patients were on background beta-blockers (higher use in the valsartan 40 BID group), 9-17% were on antiarrhythmics (higher use in the valsartan 80 BID group) and 8-11% were on calcium channel blockers. About 6% of placebo patients and about 2-5% of valsartan patients were on alpha-adrenergic blockers (the sponsor noted a statistically significant difference). About 54-57% carried an etiologic diagnosis of coronary

heart disease, 21-34% idiopathic cardiomyopathy, 7-12% hypertension, and 5-9% other. About 59-63% had no previous hospitalization for CHF. There were no differences between the treatment groups in NYHA Class, etiology of CHF, or prior CHF hospitalization.

The mean baseline LV ejection fraction was 25-27%. About 36-42% had a baseline LV ejection fraction < 25%; about 58-64% had a corresponding baseline LV ejection fraction ≥ 25%.
Mean age was about 62-64 years. Mean height was 172-173 cm and mean weight was 84-86 kg. Mean duration of CHF was 4.0-4.4 years (range (0.1-26.6 years)). No meaningful differences were seen across treatment groups.

Mean baseline LHFQ scores were 38 (±24) for the overall score, 17 (±10) for the physical score, and 8 (± 7) for the emotional score. Overall mean baseline ETT times were 434-438 (±135-143) sec; mean baseline ETT times by age were 813 (±38) seconds for the 18-29 year age group (N=2); 520 (±156) seconds for the 30-50 year age group (N=113); and 422 (±135) seconds for the > 50 age group. There appeared to be no differences by age across treatment groups.

In terms of CHF signs and symptoms, 83-91% of patients had no paroxysmal nocturnal dyspnea, 89-91% of patients had no dyspnea at rest, 92-97% had no jugular venous distension, and 76 to 83% exhibited no third heart sound. Rales were absent in 87-90% (10-12% had basilar rales only) and edema was absent in 74-77% (11-17% had trace edema). The majority of this population had dyspnea on effort (absent in 3-7%) and fatigue (absent in 8-12%). About 58-66% had no orthopnea.
Baseline mean sitting systolic blood pressure was 121-124 (±17-18) mm Hg, sitting diastolic blood pressure was 73-75 (± 10-11) mm Hg and sitting pulse rate was 76-77 (±12-14) bpm. Baseline standing pulse rate was slightly higher (80-81 ±14-15 bpm); otherwise, results for standing vital signs were similar. Baseline CHF signs and symptoms as well as vital signs were similar across treatment groups.

At baseline, about 47-50% of those randomized were on low-dose and about 37-40% were on high-dose ACE inhibitors. Throughout the study, there appeared to be minor changes in frequency but no striking differences between the treatment groups.

Drug Exposure:
The mean and median exposures were similar across treatment groups. Drug exposure was consistent between Weeks 0 and 1, and Week 1 to 16.

Table 106.5. Patient exposure to drug (ITT:all randomized patients)

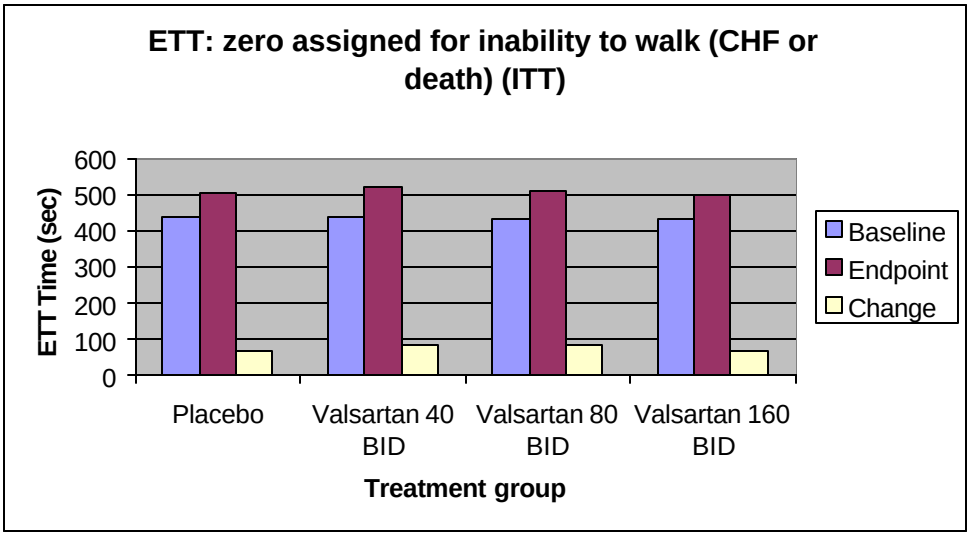
Exposure (days)	Placebo	Valsartan		
Week 0 to 16		40 mg BID	80 mg BID	160 mg BID
N	192	185	195	198
Mean (SD)	107.5 (26.7)	103.9 (31.4)	105.9 (30.9)	105.3 (29.3)
range	8-160	3-188	1-154	2-163

Efficacy:
Primary Efficacy Variables:

Over the course of this study, at least 92% of patients were able to walk. There appeared to be no meaningful differences across treatment groups in deaths or patients alive and unable to walk. Mean ETT times in all treatment groups, including placebo, improved over the course of the study.

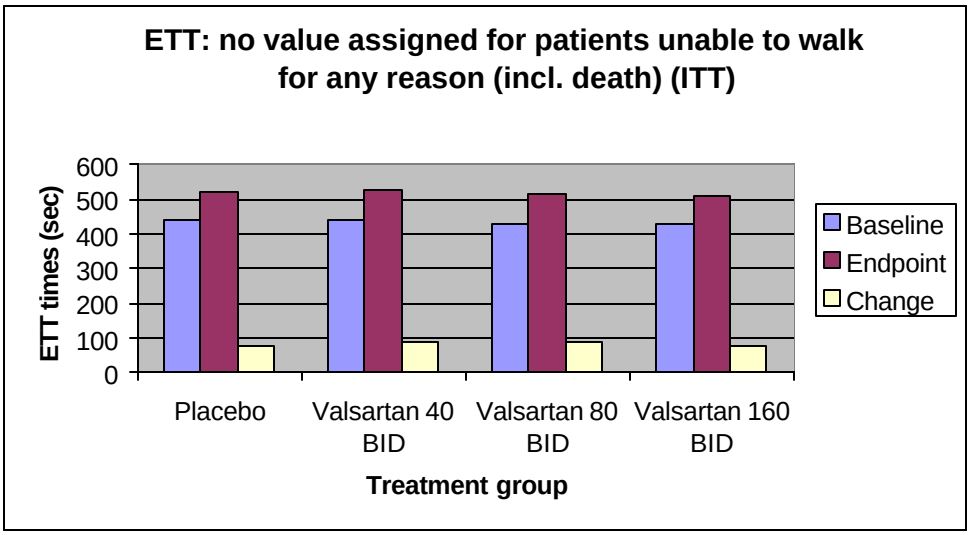
ETT: The sponsor presented the prespecified analysis, with zero assignment for inability to walk due to CHF or death, for both ITT and CAP groups. Results for the CAP were consistent with that seen in the ITT population. In addition, the sponsor presented analyses where zero was assigned for inability to walk for any reason, as well as an analysis where there was no zero assignment. Results were consistent across analyses.

Figure 106-3. ETT result: zero assigned for inability to walk due to CHF/death



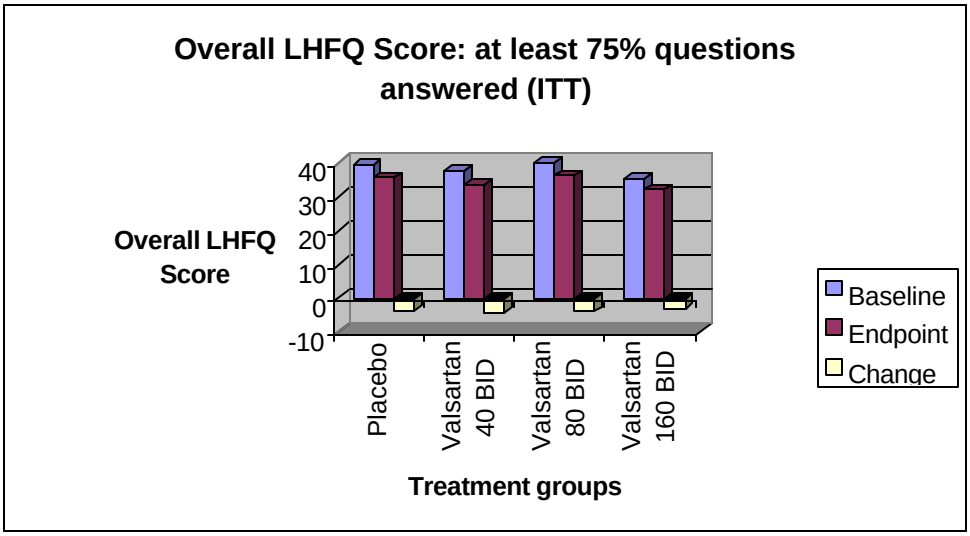
All groups, including placebo, showed statistically significant improvements in ETT time compared to baseline.

Figure 106-4. ETT result: no zero assignment



LHFQ:
Results for the overall LHFQ score are presented below, with change from baseline to endpoint. The highest baseline score was seen in the Valsartan 80 mg BID group; the largest change from baseline was seen in the Valsartan 40 mg BID group.
Results of mean change from baseline values for overall LHFQ were similar for patients with at least 1 of 21 questions answered. Results for the CAP were consistent with the ITT analysis.

Figure 106-5. Overall LHFQ Score:



Source: Volume 20, Table 9.1-5a

Table 106.6 Primary Efficacy Variable:

ANCOVA results for ETT (0 assigned for patients unable to walk due to CHF or death) and LHFQ Overall Score (≥ 75% of 21 questions answered): ITT

Between Treatment Comparison	Difference in LS means (SE of difference)	95% CI for Difference	Adjusted p value
ETT:			
40 BID vs. Placebo	19.35 (16.1)	(-12.25 50.95)	0.48
80 BID vs. Placebo	19.72 (15.8)	(-11.27, 50.71)	0.45
160 BID vs. Placebo	2.92 (15.7)	(-27.99, 33.83)	0.99
Overall LHFQ:			
40 BID vs. Placebo	-1.24 (1.5)	(-4.25, 1,78)	0.75
80 BID vs. Placebo	0 (1.5)	(-2.97, 2.97)	>0.99
160 BID vs. Placebo	-0.17 (1.5)	(-3.13, 2.80)	0.99

Source: Sponsor: Volume 20: Table 9.1-7a. Adjusted p-value based on Dunnett's procedure for multiple comparisons vs. a control.

ETT:
Results for Hochberg's step-up procedure at endpoint also showed no statistical significance. Results for CAP were consistent with the ITT analysis (ie, no significant difference for valsartan vs. placebo); it should be noted that, in the CAP analysis the placebo group did slightly better (ie, longer ETT time) than the 160 BID group at Week 12; thus, it cannot be said that valsartan group at all times showed better ETT times compared with placebo. ANCOVA results by week showed no statistically significant difference compared with placebo.

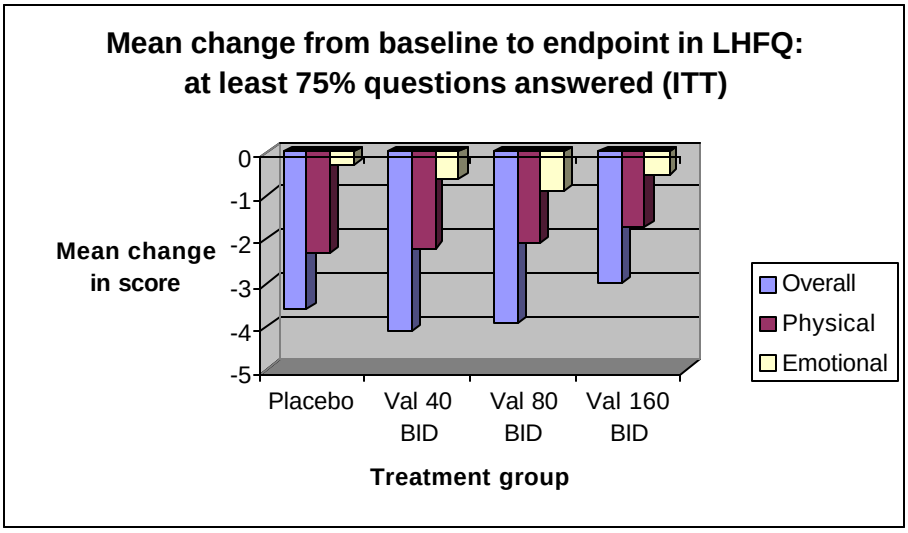
In an analysis where zero was assigned for patients unable to walk for any reason, including death, there was a trend toward statistical signficance only in the valsartan 80 BID group (adjusted p value =.056); however, this result was not seen in the higher dose group (valsartan 160 BID, adjusted p value =0.90). A pairwise-treatment-comparison for ranked ETT (residuals after baseline adjustment), controlling for background use of ACE inhibitors, showed trends toward statistical signficance in the valsartan 40 BID vs. placebo (p=0.09) and in the valsartan 80 BID vs. placebo (p=0.06) in favor of valsartan; however, the favorable trend was much smaller in the valsartan 160 BID vs. placebo group(p=0.74).

A subgroup analysis of ETT results by background ACE (y/n), beta blockers (y/n), age <65 vs. 65 years and older, gender and CHF etiology was presented by the sponsor. However, because of the differences in sample size (for example, the N per each treatment group for females=32-38 compared to the N for males=133-148; the N not taking ACEI =19-28 and the N on ACE=149-156) as well as baseline ETT differences make subgroup interpretation difficult.

Secondary Efficacy Variables:

Change from baseline in emotional and physical scores of the LHFQ:
Results are shown below (see Figure). Greater decreases with valsartan, compared to placebo, can be seen with the changes in emotional score, but not overall or physical score.

Figure 106.6. Change in LHFQ Scores from baseline to endpoint (ITT)



Source: Volume 20, Table 9.1-5a, 9.2-1a, 9.2-1b

Change from baseline in EF:
A statistically significant increase in ejection fraction from baseline to endpoint can be seen (Table 106.7) for valsartan vs. placebo.

Table 106.7. ANCOVA pairwise-treatment comparison results for change from baseline at endpoint in LV EF (ITT)

Treatment group	N	LS mean	LS mean difference (SE) from placebo	95% Confidence Interval for LS mean difference from placebo	p-value
Placebo	169	1.31	--	--	--
Val 40 mg BID	150	3.02	1.71 (0.85)	(0.05, 3.38)	0.0437*
Val 80 mg BID	168	2.72	1.41 (0.82)	(-0.20, 3.01)	0.0856
Val 160 mg BID	167	3.90	2.59 (0.82)	(0.97, 4.20)	0.0017*

Source: Sponsor, Volume 20, Table 9.5. N=number of patients with values at baseline and endpoint.
*=statistically signficiant at the 0.05 level

NYHA Class and Signs/Symptoms of CHF are listed in Table 8 as % improved and worsened from baseline to endpoint. For NYHA Class, the trends in improvement and worsening favored valsartan; however, pairwise treatment comparisons, controlling for baseline values and background use of ACE inhibitors, showed no statistically significant differences between valsartan and placebo at endpoint.
The results of changes in signs/symptoms of CHF were inconsistent.
Dyspnea on effort and fatigue, the two most prevalent signs and symptoms in this study population, showed greater improvement in the valsartan groups; dyspnea on effort also showed the highest percent worsening in the valsartan 80 BID group. For PND, edema, third heart sound and rest dyspnea, the placebo group showed the greatest improvement; for PND and rest dyspnea, the highest dose of valsartan showed the greatest worsening. No statistically significant differences were noted at endpoint (when analyzed as pairwise treatment comparisons, controlling for baseline values and background ACE inhibitor use).

Table 106.8. NYHA Class and Signs/Symptoms: Percent ITT who improved/worsened (at endpoint)

	Placebo N=192 %N	Val 40 BID N=185 %N	Val 80 BID N=195 %N	Val 160 BID N=196 %N
NYHA:				
Improved	19.8	20.5	24.1	21.9
Worsened	8.3	4.9	5.6	5.6
PND:				
Improved	11.5	8.1	9.2	6.6
Worsened	3.1	2.2	3.6	5.1
Dyspnea at rest:				
Improved	7.3	7	7.7	5.6
Worsened	4.7	4.3	4.6	5.6
Dyspnea on effort:				
Improved	33.8	37.8	36.9	35.2
Worsened	15.1	15.7	17.4	15.8
Fatigue:				
Improved	33.3	32.4	35.4	36.2
Worsened	21.9	20.5	18.5	20.9

Orthopnea:				
Improved	13.5	16.8	19	18.4
Worsened	6.8	8.6	6.2	8.2
JVD:				
Improved	4.2	4.3	4.1	1.5
Worsened	4.2	1.6	2.1	1.5
Edema:				
Improved	13.5	13.0	12.8	13.3
Worsened	12.5	9.7	13.8	8.2
Rales:				
Improved	5.7	7.0	5.1	6.6
Worsened	6.3	5.4	6.7	1.5
Third heart sound				
Improved	10.4	9.7	8.2	8.6
Worsened	6.8	4.9	4.6	3.5

Source: Volume 20: Table 9-6

Safety:

Table 106.9. Number (%) of patients who died, had other serious or clinically significant AE or discontinued due to AE (Safety analyzable population)

	Placebo N=192	Val 40 BID N=185	Val 80 BID N=194	Val 160 BID N=197
Deaths	6 (3.1)	2 (2.2)	2 (2.1)	5 (2.5)
All SAE	30 (15.6)	27 (14.6)	27 (13.9)	21 (10.7)
Discontinued due to AE	9 (4.7)	20 (10.8)	17 (8.8)	21 (10.7)
Discontinued due to SAE	5 (2.6)	6 (3.2)	8 (4.1)	7 (3.5)
Discontinued due to lab abnormality	0	0	0	2 (1.0)

Source: Volume 20: Table 10-8. Deaths include patients who died during double-blind, and those who died within 30 days after completing or discontinuing study.

Deaths:
A total of 20 patients died: one patient died during the placebo run-in, 11 patients died during the double-blind period, and 8 patients died either after premature discontinuation or within 30 days after completing the study.

For further safety discussion, please see the Integrated Summary of Safety.

Conclusions:
1. There were no significant improvements in baseline ETT or overall MHFQ to endpoint with valsartan compared to placebo.
2. Compared to placebo, there was a significant increase in LV ejection fraction in the valsartan groups.

Study 107: Multicountry, randomized, double-blind, parallel, placebo-controlled trial to assess the effect of valsartan on morbidity and mortality, signs and sympbtoms, and quality of life in patients with stable, chronic congestive heart failure (NYHA Class II-IV) (Phase III)

Source: NDA 20-665, S-016: Volume 57 (Protocol); Volume 28 (Study Report); electronic database.

Sites: 302 centers in 16 countries (Europe, South Africa, Australia, and USA).

Study Duration: March 27, 1997 (first patient enrolled) to October 5, 2000 (last patient completed).

Objective: To assess the effect of valsartan, in comparison with placebo, on morbidity and mortality, signs and symptoms, and quality of life in patients with stable, chronic congestive heart failure (NYHA Class II-IV).

Primary Efficacy Variables: 1. Time to death; and 2. Time to first occurrence of a morbid event (morbid event: death, sudden death with resuscitation, need for therapeutic doses of an intravenous intropic or vasodilating agent for congestive heart failure (CHF) for at least 4 hours, or hospitalization for CHF).

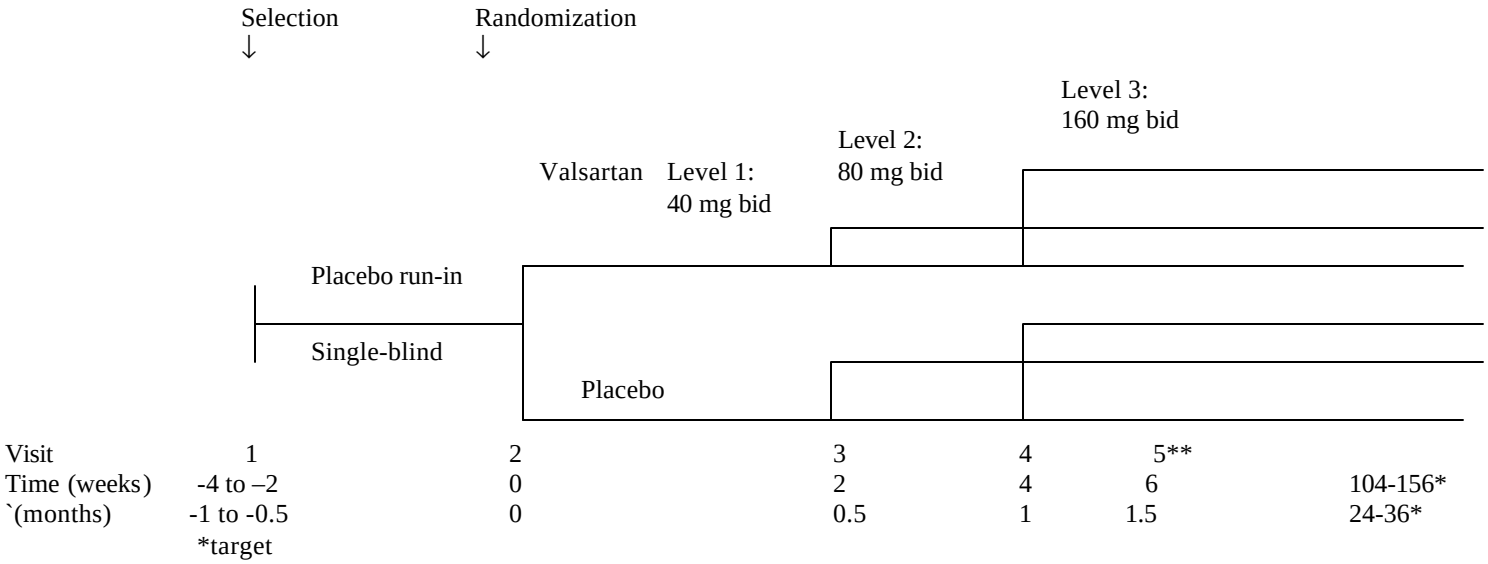
Secondary Efficacy Variables: 1. Time to first occurrence of a morbid event other than death (morbid event defined as above); 2. Time to hospitalization for CHF (first occurrence); 3. Time to cardiovascular-related death; 4. NYHA classification; 5. Signs/symptoms of CHF (paroxysmal nocturnal dyspnea, fatigue, edema, dyspnea at rest, dyspnea on effort, othopnea, jugular venous distension -45°, rales, third heart sound); 6. Change from baseline in ejection fraction; 7. Change from baseline in LV internal diastolic diameter (LVIDD); 8. Change from baseline in overall, physical, and emotional scores for the Minnesota Living with Heart Failure quality of life questionnaire.

Design: This was a randomized, double-blind, forced titration, event-driven, parallel, placebo-controlled trial. Patients were to receive valsartan or placebo, as shown in Figure 1, in addition to standard CHF background therapy. Randomized patients were stratified according to their use of beta blockers.
The trial was to continue, with all randomized patients remaining in the trial, until 906 deaths occurred or statistically significant results were observed for either of the two interim analyses (see Protocol Amendment #3 regarding modification of interim analysis). The scheduled time for enrollment was 12 months and the targeted duration of double-blind treatment was 24-36 months.

At Visit 2, patients were stratified according to their use of beta blockers and randomized to receive either valsartan 40 mg bid or matching placebo. Patients were then up-titrated at Visits 3 and 4. Those who could not tolerate the highest dose of valsartan were to be titrated down to the next lower dose after 2 weeks of treatment (Visit 5). The criteria for titration (Visits 3, 4, 5) were: persistent standing systolic BP $\geq$ 90 mm Hg AND no symptoms of hypotension (i.e. syncope, faintness, orthostatic dizziness) AND no increase in serum creatinine > 50% from baseline to a value > 2.0 mg/dl (see Protocol Amendment #2). If patients did not meet all three

criteria, they were either down-titrated to the previous dose level or discontinued from trial treatment from lowest possible dose level. If up-titration could not be performed due to a temporary medical condition, an attempt to reach the highest tolerated dose level was made, if medically acceptable, after Visit 5. When a patient was up-titrated after Visit 5, laboratory testing was done after 2 weeks of exposure to the higher dose level.

Figure 107-1. Study Design (107)



**Visits continue past Visit 5. Please see Table 1 (Schedule of Procedures) below

Inclusion Criteria:

1. Males or females; minimum 18 years old, with CHF (NYHA Class II-IV) beginning at least 3 months prior to Visit 1. Females of childbearing potential were to use effective forms of contraception with negative preganancy tests throughout the study.
2. Ejection fraction < 40% on echocardiography and left ventricular internal diameter in diastole > 2.9 cm/m^2 on echocardiography within one week prior to Visit 1 or during the placebo run-in period.
3. Stable dosage regimen of CHF medication for two weeks prior to Visit 1 and during the placebo run-in period.
4. Willingness to provide informed consent.

Exclusion Criteria:

1. Pregnant, nursing or women of childbearing potential not practicing effective contraception.
2. Right heart failure due to pulmonary disease.
3. Postpartum cardiomyopathy.
4. Rapidly deteriorating heart failure.
5. Unstable angina, stroke, myocardial infarction or cardiac surgery, including percutaneous transluminal coronary angioplasty (PTCA) within past 3 months.

6. History of heart transplant or those patients who are on transplant list.
7. Coronary artery disease likely to require coronary artery bypass graft (CABG) or PTCA.
8. Sustained ventricular arrhythmia with syncopal episodes within past 3 months that is untreated.
9. Hemodynamically significant mitral stenosis or mitral regurgitation (MR), except MR secondary to left venticular (LV) dilatation.
10. Hemodynamically significant obstructive lesions of LV outflow, including aortic stenosis.
11. Persistent standing systolic blood pressure < 90 mm Hg.
12. Primary liver disease considered to be life threatening.
13. Renal disease likely to be life threatening or serum creatinine > 2.5 mg/dl.
14. Malignancies likely to limit 5 year survival.
15. History or presence of any other disease with a life expectancy of < 5 years.
16. Contraindication to the use of angiotensin II receptor antagonists.
17. Prior or current double-blind treatment in valsartan CHF trials.
18. Participation in an investigational drug study within the past 30 days.
19. Any condition that would jeopardize evaluation of efficacy or safety.
20. History of noncompliance/considered potentially unreliable.
21. Treatment with any of the following within the past 3 months prior to Visit 1: Class IC antiarrhythmic agents (such as flecainide and propafenone), chronic intermittent intravenous inotrope or intravenous vasodilator therapy, angiotensin II receptor antagonists (including valsartan).

Concomitant medications:
As noted above, patients were to be on stable doses of medications for CHF for at least 2 weeks prior to Visit 1. Medications for CHF that were allowed as background therapy included diuretics, ACE inhibitors, digoxin, hydralazine, nitrates, and antiarrhythmics (except Class IC agents).

Table 107.1. Schedule of Procedures (107)

Visit	1	2	3*	4*	5	6	7	8	9	10	11	12	13	14-18H
Month	-1 to -0.5	0	0.5	1	1.5	2	4	6	9	12	15	18	21	24-36
Physical Exam/Sympt. review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray	X									X				X
LVEF/LVIDD	X						X			X		X		X
ECG	X	X					X			X				X
Heart Failure QoL questionn.I	X	X		X			X	X	X	X	X	X	X	X
Morbid event		X	X	X	X	X	X	X	X	X	X	X	X	X
AE/ con med	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoecon.		X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory**	X	X	X	X	X		X			X		X		X
Neurohormones		X					X***			X***				X***
Trial medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X#

*Up-titration visits **hematology, blood chemistry, urinalysis, pregnancy test ***only norepinephrine
#except at final visit.
H Visits at 3 month intervals; procedures for Visits 15 and 17 are same as Visit 11; procedures at Visit 16 as for Visit 12; procedures at Visit 18 as for Visit 10.
I The Minnesota Living with Heart Failure Questionnaire was used in selected countries.

Withdrawal criteria:

Patients were withdrawn from the trial:

- Whenever the patient or investigator decided that it was in the patient's best interest.
- Intolerable adverse experiences
- Life-threatening laboratory abnormality despite manipulation of trial therapy and/or background treatment
- Positive pregnancy-test results in a patient who decides to carry pregnancy to term.

Patients were to be removed from trial treatment if, after alteration of dose level and background treatment, the persistent standing systolic BP < 80 mm Hg, or there were symptoms of hypotension. Patients still alive at the time of premature discontinuation from double-blind treatment were to continue to visit the investigator according to the protocol until trial end.

Statistical Methods:

Two primary efficacy endpoints were analyzed for this trial: time to death and time to first occurrence of a morbid event. To achieve an overall significance level ≤ 0.05 (two-sided), an adjustment for two primary endpoints was made, with each primary endpoint tested at a 2-sided significance level of 0.02532 based on Dunn-Sidak inequality. The null hypothesis tested was that median survival time to the primary endpoint of death is the same for valsartan and placebo. The alternative hypothesis was that the median suvival time for valsartan is different from that of placebo.

Three analyses of the primary endpoint time to death were initially planned: two interim and one final analysis. The Lan-DeMets alpha-spending function with a O'Brien-Fleming group-boundary was used. It was assumed that these three analyses were to be equally spaced (based on the accumulated total number of patient deaths prior to permanent discontinuation from treatment for both treatment groups). The interim analyses, according to the protocol, were planned to occur when a total of 302 and 604 deaths (prior to permanent discontinuation from trial treatment) occurred.

A total of 906 patient deaths for both treatment groups combined was needed for the primary efficacy analysis, except in the case of significant interim findings. The number of patient deaths is calculated to have statistical power of 90% (or more) for each primary endpoint, assuming an annual death rate for placebo of 12% (i.e., median survival time of 5422 years) and an annual rate of 9.6% for valsartan (i.e., median survival time of 6868 years). The annual event rate of 9.6% for valsartan was based on detecting a 20% reduction from the annual event rate for placebo. The sample size was determined by the number required to achieve 906 patient deaths. It was estimated that approximately 3660 completed patients, 1830 per treatment arm, would be required. Assuming a discontinuation rate of 15%, it was estimated that 4310 patients, 2155 per treatment arm, would be required. Since death is a component of morbid events, the sample size planned was also to be adequate for the analysis of time to morbid event.

According to the protocol, comparability among treatment groups was to be examined for the following:

- Race (White, Black, Other)
- Gender
- Significant medical history/concomitant diagnosis (yes or no)
- CHF etiology (ischemic/non-ischemic)
- Background Antiarrhythmic treatment at baseline (yes or no)

- Background uses of digoxin at baseline (yes or no)
- Background use of diuretics at baseline (yes or no)
- Background use of beta-blockers at baseline (yes or no)
- Background ACE inhibitor therapy at baseline (yes or no)
- Previous hospitalization for CHF (yes or no)

The Cochran-Mantel-Haenszel chi-square test was to be used for this analysis.

Comparability among treatment groups for all randomized patients was to be examined using the F-test for the baseline values of: age, height, weight at Visit 1, duration of CHF

The log rank test was to be performed as the primary for the survival analysis of time to death and time to morbid event. A supplementary Cox-regression analysis of the primary endpoints was also to be performed for robustness purposes and to explore potential prognostic factors. Major prognostic factors for the Cox regression analysis was to be determined prior to data analysis. Prognostic factors to be considered for this analysis include country, baseline NYHA classification, use (yes/no) of beta-blocker at baseline, CHF etiology (ischemic/non-ischemic), baseline neurohormone levels, and age (or age group).

Safety Evaluation: included adverse event monitoring, laboratory measurements, and vital signs.

Protocol amendments: (The original protocol was dated 8-5-96.)

1. Amendment #1: (dated 1-14-97): modified 2 exclusion criteria, established procedures for titration to the highest possible dose if not possible between visits 2 to 5, included triglycerides as part of routine laboratory testing, included measurements of BNP (brain natriuretic peptide) at Visits 7, 10, and annually thereafter, and to permit recording of signs/symptoms of CHF as a scoring system.
2. Amendment #2: (dated 11-17-97): modified creatinine titration criterion for valsartan, adding the phrase "to a value > 2.0 mg/dl.
3. Amendment #3: (dated 2-23-98) modified the interim analysis to include both primary variables; in addition, interim analyses were changed from 3 equally spaced to approximately every 6 months, beginning around March, 1998, allowing modifications when warranted, based on trial progress and DSMB meetings. The interim analysis was to be performed by a Novartis statistician who is independent of the trial. In addition, the requirement for patient death to occur "prior to discontinuation from double-blind medication" was eliminated.
4. Amendment #4: (dated 3-27-00) modified procedures for the final study visit, clarified definition of trial completion date, and defined analysis of morbid/mortal events after occurrence of the 906th patient death.
5. Amendment #5: (dated 4-10-2000) offered patients who completed the final visit of the core study the opportunity to continue double-blind treatment for another 4-6 months until the database was complete and unblinded. This was conducted on a compassionate use basis with no planned efficacy analyses.

Monitoring committees:

- Data and Safety Monitoring Board (DSMB):
  Committee Members:
  William Parmley, MD (USA)
  Jonathan Abrams, MD (USA)
  Marco Bobbio, MD (Italy)
  David DeMets, Ph.D (USA)
  Dirk van Veldhuisen, MD (Netherlands)

Reviewer's Comment: DSMB minutes were requested by the Agency. According to the Sponsor, minutes were not kept and there are no available notes. According to the Study report, the DSMB was to review serious adverse events and other safety parameters in a "semi-blinded fashion." According to the sponsor, the independent Novartis statistician (who was responsible for performing and reporting the interim analyses to the DSMB) physically attended one meeting and was available by phone for the other meetings. This independent statistician was the only person with access to the randomization codes.

The medical reviewer is unable to verify the DSMB process or extent of unblinding.

- Endpoint committee: According to the sponsor, this committee provided independent, blinded assessment of efficacy endpoints (all cause mortality, sudden death with resuscitation, need for therapeutic doses of an intravenous inotropic or vasodilating agent for CHF for at least 4 hours, cardiovascular-related deaths) as defined in the protocol, based on standardized classifications and definitions.

  Endpoint Committee Members:

  Peter Carson, MD (USA)
  Christopher O'Conner (USA)
  Cristina Opasich, MD (Italy)
  Ileana Pina, MD (USA)
  Marino Scherillo, MD (Italy)
  Gianfranco Sinagra, MD (Italy)
  Felix E. Tristani, MD (USA)
  Alberto Volpi, MD (Italy)
  Lynne Warner Stevenson, MD (USA)

Dr. Volpi was also responsible for one of the three echocardiogram laboratories (see below). According to the Endpoint Committee Manual (dated December 6, 1998), each potential endpoint was to be independently assessed by two members (from the US and Europe, respectively). The results of these assessments was to be presented to the full committee by one of the evaluators and a final decision was to be made by majority vote. The sponsor provided a package of information regarding efficacy endpoints with documentation in English**.**

- **The sponsor screened all hospitalization endpoints; hospitalizations that did not meet endpoint criteria (i.e., scheduled, elective, or clearly non-cardiovascular) were not submitted to adjudication. For non-scheduled hospitalizations with clearly non-cardiovascular conditions, the sponsor provided only a narrative summary to the committee chair.**
- "Hospitalization" was defined as an overnight stay even if the total duration of time was < 24 hours; overnight stays in emergency rooms or observation units were included in this category. Hospitalizations for CHF treatment-related complications were not included in this category.
- In an addendum to the Endpoint Committee Manual, dated April 4, 2001, it was defined that an admission due to overdiuresis or drug toxicity was to be classified as a "hospitalization for reasons other than heart failure"; also listed in this category was cardiac decompensation that did not meet the heart failure definition. Hospitalizations that were clearly less than 24 hours were not submitted as events. If it could not be clearly determined that a patient was hospitalized for less than 24 hours, and there was a change in days, the case was adjudicated.

- The Endpoint Committee was supplied with the SAE report, hospitalization records as available, investigator narratives when applicable and CRF printout. The Endpoint Committee did not make determination of CV relation.
- The Endpoint Committee met 15 times. A planning meeting was held in March, 1997. The first adjudication meeting was held in December, 1997. Three meetings were held in 1998, five during 1999, and five meetings in 2000.

Reviewer's comments:
1. The diagnoses of "overdiuresis" and "drug toxicity" were not further defined in the Endpoint committee manual.
2. From two to four representatives of the sponsor attended the Endpoint Committee meetings. According to the sponsor, the role of these representatives was to handle logistics and record adjudications issued by the committee.
3. In a meeting with the sponsor, the sponsor claimed that "all endpoints" were adjudicated. Since the written definition appears to be different, the Agency requested written clarification as to the exact adjudication process, i.e., what information from the first hospitalization endpoint was sent to the Endpoint Committee.

- Steering committee: ethical, scientific and policy decisions regarding conduct of the trial; act upon recommendations of the Endpoint Committee and DSMB. One or more Novartis staff members attended all meetings.

Members: Jay Cohn, MD (Study Chairman) (Minneapolis, MN, USA)
Gianni Tognoni, MD (Italy)
Inder Anand, MD (USA)
Antoni Bayès de Luna, MD (Spain)
Csaba Farsang, MD (Hungary)
Torben Haghfelt, MD (Denmark)
Christer Höglund, MD (Sweden)
Niklas Holwerda, MD (Netherlands)
Henry Krum, MD (Australia)
Phillippe Lechat, MD (France)
Silja Majahalme, MD (Finland)
Lionel Opie, MD (South Africa)
Klaus Stumpe, MD (Germany)
Lip Bun Tan, MD (Great Britain)
Luigi Tavazzi, MD (Italy)
Johan Vanhaecke, MD (Belgium)
Arne Westheim, MD (Norway)
Jiri Widimsky, MD (Czech Republic)

Drs. Widimsky, Vanhaecke, Haghfeldt, Majahalme, Krum, Farsang, Tavazzi, Holwerda, Westheim, Bayes de Luna, Hoglund, Tan and Anand are also Investigators for 107.

- Executive committee

Members: Jay Cohn, MD (USA)
Gianni Tognoni, MD (Italy)
Robert Glazer, MD (Novartis; USA)
Dirk Spormann, Ph.D. (Novartis; Switzerland)

- Echo laboratories:

Alberto Volpi, MD (Italy)
Christer Hoglund, MD (Sweden)
Maylene Wong, MD (USA)

Dr. Hoglund was one of the Investigators. Dr. Volpi was a member of the Endpoint Committee.

Interim Analyses Results:

Five interim analyses were performed biannually. More precisely, the total number of deaths at the interim analyses were 38, 141, 368, 595, and 748, respectively. Table 107.2 presented the interim results. Clearly, there was no statistical evidence for the valsartan effect on mortality. The trial end date was May 3, 2000 which was determined as the date by which 906 deaths were recorded and a letter was sent out to declare and document the trial end as soon as 906 deaths were observed on May 3, 2000. There were 979 deaths between May 3, 2000 and locking the database. In the final analysis of time to death at the trial end, the significance level was adjusted according to the planned Lan-DeMets spending function, using the information times based on 38, 141, 368, 595, 748, and 979 deaths. Thus, the primary analysis at trial end was performed at a two-sided significance level of 0.02.

Table 107.2 . Interim results

Interim Analysis No.	Hazard ratio (95% CI)	Value of log rank test	Value of rejection boundary for valsartan efficacy
1	0.60 (0.31, 1.16)	1.53	5.00
2	0.93 (0.67, 1.30)	0.42	5.00
3	0.97 (0.79, 1.19)	0.32	3.75
4	0.99 (0.84, 1.16)	0.15	2.87
5	0.95 (0.83, 1.10)	0.65	2.55

Source: Sponsor's results

Interim analyses of time to first morbid event were performed concurrently with interim analyses for time to death. However, no upper boundary was considered for time to first morbid event because interim analysis results for this variable were not used to claim efficacy, but were only used to aid in determining whether to terminate the trial due to lack of efficacy with valsartan (the same lower boundary as that using the opposite of the upper boundary for time to death was used). Therefore, no further statistical adjustment was made for this variable and the final analysis of time to first morbid event was performed at the significance level of 0.02532.

Primary and secondary variable, treatment group comparability with respect to demographics, background medication and baseline data, serious adverse events, specified laboratory variables, blood pressure, and reasons for discontinuation.

Results:

Of those randomized, 43-44% of each treatment group were from sites in the United States; after the United States, 14% of patients in each group were entered from sites in Italy, and 11% in each group from sites in the Netherlands.

Table 107.3. Patient Disposition (107)

	Valsartan n (%)		Placebo n (%)		Total n (%)	
Enrolled					5984	
Randomized	2511	(100)	2499	(100)	5010	(100)
Completed (to death or trial end)	2487	(99)	2466	(99)	4953	(99)
Discontinued:	24	(1.0)	33	(1.3)	57	(1.1)
Heart transplant	18	(0.7)	23	(0.9)	41	(0.8)
Other	6	(0.2)	10	(0.4)	16	(0.3)
Lost to f/u	3	(0.1)	4	(0.2)	7	(0.1)
Permanently discontinued from study treatment	448	(18)	339	(14)	787	(16)
Adverse experience	215	(9)	136	(5)	351	
Life-threatening lab abnormality	34	(1.4)	10	(0.4)	44	
Persistent SSBP < 80 mm Hg or signs of hypotension	30	(1.2)	11	(0.4)	41	
Other	169	(7)	182	(7)	351	(7)
Discontinued from run-in	--		--		974	(16)
Death	--		--		21	(0.4)
Heart transplant	--		--		2	(<0.1)
other	--		--		947	(16)
Reason missing					4	(0.1)

Source: Sponsor—Volume 28, Section 7

Of the 2511 patients in the valsartan arm and the 2499 patients in the placebo arm, 23% and 24%, respectively, were noted to have protocol violations. Of these, 3% were considered to be major protocol violations and 21% were minor protocol violations; there were no meaningful differences between the two treatment groups.

Three patient populations were identified: the intent-to–treat (ITT) group; the Safety Analyzable Population (SAP), or those who received drug and for whom safety data are available; and the Clinically Assessable Population, or the ITT group excluding major protocol violators.

Table 107.4. Patient populations (107)

	Valsartan		Placebo		Total	
Patients randomized	n 2511	% 100.0	n 2499	% 100.0	n 5010	% 100.0
ITT	2511	100.0	2499	100.0	5010	100.0
SAP	2506	99.8	2494	99.8	5000	99.8
CAP	2441	97.2	2419	96.8	4860	97.0

Source: Sponsor—Volume 28, Section 7

Baseline Characteristics:
The randomized population was 80% male and 20% female, about 90-91% Caucasian, 7% Black and 3% Oriental; about 52-52% were below 65 and 46-48% were 65 and older. Mean age was 62-63 (± 11) years old; the ages ranged from 18 to 96 years old. Mean height was 171 (± 9 cm), mean weight was 79-80 (± 15-16) kg and mean duration of CHF was 51 months (with a median of 36 and range from 1 to 660 months). Mean sitting systolic Blood Pressure (SBP) was 124 (± 18-19) mm Hg , mean sitting diastolic BP was 76 (± 11) mm Hg and sitting pulse rate was 73-74 (±13) beats/minute. Standing blood pressures and pulse rates yielded similar results. There were no meaningful differences between the two treatment groups.

The most common baseline symptoms reported were dyspnea on effort (absent in only 5%) and fatigue (absent in 16-17%). Most patients (> 70 %) had no jugular venous distention, orthopnea, paroxysmal nocturnal dyspnea, dyspnea at rest, rales, or a third heart sound. Edema was absent in 82-83% of patients. No differences between the two treatment groups were noted.

Over 90% of the randomized patients were on baseline ACE inhibitors and about 85-86% were on diuretics. A little over one-third were on baseline beta blockers and less than half were on nitrates. A review of the individual beta blockers, diuretics, ACE inhibitors, calcium channel blockers and nitrates at baseline revealed no difference in use between the two treatment groups.

Table 107.5. Baseline characteristics (all randomized patients) (107)

		Valsartan		Placebo	
		n	%	n	%
Randomized		2511	100	2499	100
NYHA Class	I	2	0.1	3	0.1
	II	1560	62	1535	61
	III	907	36	906	36
	IV	42	2	55	2
Background treatment	Amiodarone	322	13	332	13
	Digoxin	1685	67	1689	68
	Diuretics	2154	86	2128	85
	Beta-blockers	867	35	883	35
	ACE inhibitors (ACEI)	2326	93	2318	93
	Nitrates*	986	39	957	38
	Calcium channel blockers	289	12	320	13
ACEI/beta blocker (BB) at baseline	BB and ACEI	794	32	816	33
	Neither BB nor ACEI	112	5	114	5
	ACEI but no BB	1532	61	1502	60
	BB but no ACEI	73	3	67	3
Etiology	Ischemic	1446	58	1419	57
	Idiopathic cardiomyopathy	780	31	780	31
	Hypertension	154	6	183	7
	Other	131	5	117	5

Source: Sponsor: Volume 28: 7.4.2 *Long and short-acting

Baseline LV measurements (ITT) revealed the following: mean (and median) ejection fraction (EF) of 27% (±7) with a range of approx. 4-55%; mean LV internal diastolic diameter (LVIDD) of 6.9 (± 0.9) and mean LVIDD/BSA of 3.6-3.7 (±0.5) cm/m^2. Approximately 48% and 47% of all randomized patients in the valsartan and placebo groups, respectively, had baseline LV EF meaurements less than the median value. The Minnesota Living with Heart Failure questionnaire (LHFQ) baseline results revealed a mean overall score of 32-33 (± 23), mean physical score of 14-15 (±11), and mean emotional score of 6.8 (± 7). There were no meaningful differences between the two treatment groups.

Of the baseline neurohormone measurements, only mean aldosterone levels showed a statistically significantly different ($p < 0.05$), higher in the placebo group.

Table 107.6. Baseline neurohormone measurements (all randomized patients):

Neurohormone		Valsartan (N=2511)	Placebo (N=2499)
Norepinephrine (pg/ml)	N (non-missing)	2141	2160
	Mean (±SD)	456 (270)	472 (368)
Brain natriuretic peptide (pg/ml)	N (non-missing)	2145	2160
	Mean (±SD)	184 (231)	178 (230)
Aldosterone (pg/ml)	N(non-missing)	2114	2126
	Mean (±SD)	132 (118)	140 (137)
Plasma renin activity (ng/mL/h)	N(non-missing)	2141	2150
	Mean (±SD)	15 (24)	14 (24)
Endothelin I (fmol/mL—US patients)	N(non-missing)	964	970
	Mean (±SD)	2 (1.7)	1.9 (1.6)
Big endothelin (fmol/ml) –non-US patients	N(non-missing)	1180	1179
	Mean (±SD)	1 (0.7)	1 (0.6)

Source: volume 28, Table 7.4-9

Patient Exposure:
Tables 107.7 and 8 summarize exposure to valsartan monotherapy:

Table 107.7. Minimum exposure to therapy by Total Daily Dose of Valsartan (all randomized)

Exposure to Valsartan (days)	Valsartan (mg/d)				
	0	80	160	320	Any dose>0
>1	1170	2508	2345	2120	2508
>30	533	449	526	1947	2412
>60	358	310	396	1900	2325
>90	221	276	343	1852	2268
>180	67	223	268	1693	2156
>360	9	162	199	1544	1968
>720		69	78	724	1063

Source: Sponsor: Volume 28: section 8, Table 8.1-1a

Table 107.8. Patient exposure (Summary)

Total number of patients on Valsartan	2511
Range of Duration on Valsartan (days)	1 to 1203
Mean Duration on Valsartan (days)	604
Mean daily dose of valsartan (mg)	254

Between Months 1 and 30, at least 70% of randomized patients were on a total daily dose of 320 mg.

EFFICACY RESULTS

Time to event variables were derived from the event date on the Endpoint Committee Form and not from investigators' event dates. Censoring times were determined from CRF page 106 (heart transplant, lost to f/u), page 105 (date of last medication taken=date of treatment discontinuation) or from analysis cut-off date of May 3, 2000. For time to event variables, endpoint was determined as the last available value before the cutoff of May 3, 2000 (whether or not event occurred before or after permanent discontinuation of study treatment). The time to event was considered censored for: patients discontinued from the trial due to heart transplant with no events observed prior to heart transplant (time from randomization to date of heart transplantation (if known) or date of final visit (if heart transplantation date unknown); patients completing trial with no observed events; or patients lost to follow-up with no events observed. In those patients, time to censoring was the time from randomization to completion, or analysis cut-off date, or date of lost to follow-up. There was no adjudication on mortality/morbidity endpoints at trial end (May 3, 2000); all patient deaths and dates from trial end to trial completion (last patient, last visit) were recorded by the investigators.

For the two primary endpoints, the sponsor presented the p-value of logrank test and the hazard ratio and its confidence interval based on the analysis adjusted for various covariates (e.g., NYHA Class III vs. (II & I), NYHA Class IV vs (II & I), LVEF < median value, ACE inhibitor at baseline, beta blocker at baseline, etiology, age category). Thus, in some instances the 95% confidence interval of hazard ratio contained one but the logrank p-value is much less than 0.05. Such presentation is not desirable. For secondary endpoints, the sponsor presented the results of analyses adjusting for various baseline covariates, pooled centers, and treatment by covariate interactions.

In this review we presented the results with no adjustment for covariates in all endpoints. For secondary endpoints, the results in our tables were based on the analysis using last available post-randomization value to compute the change from baseline. Our results and the sponsor's results are qualitatively similar.

As summarized in Tables 107.9 and 107.10, the time to censoring for the primary adjudicated morbid events and for the non-fatal morbid events appeared to be balanced between the two treatment groups.

Table 107.9. Distribution of time to censoring for primary morbid events

		Valsartan (N=2511)	Placebo (N=2499)
# of events		723 (28.8%)	801 (32.1%)
# censored		1788 (71.2%)	1698 (67.9%)
IN DAYS	Max	1112	1108
	95th-tile	1028	1031
	90th	981	980
	75th	891	888
	Median	758	751
	Mean	743	742
	25th	575	574
	10th	499	500
	5th	478	479
	Min	68	26

Primary morbid events: death, sudden death with resuscitation, therapies for CHF, CHF hospitalizations

Table 107.10. Days at risk for non-fatal morbid events

		Valsartan (N=2511)	Placebo (N=2499)
IN DAYS	Max	1111	1118
	95th-tile	1022	1023
	90th	965	965
	75th	870	866
	Median	715	719
	Mean	681	680
	25th	518	527
	10th	384	378
	5th	195	179
	Min	2	1

Days at risk = time to death for deaths and time to last follow-up for survivors.

It can be seen from Table 107.11 that there was no survival benefit in the valsartan group, either for all-cause or CV deaths. In fact, the frequency and hazard ratios trend slightly in favor of the placebo group. For non-fatal morbid events, results significantly favor the valsartan group. This composite endpoint appears to be "driven by" the results of CHF hospitalization, where the data significantly favor the valsartan group (the effect size of the category "Sudden Death with

Resuscitation" may also contribute to the favorable valsartan effect; however, the event rates are relatively small). From Figures 38 and 39, the log(-log(time-to-event)) curves were parallel during the most part of study duration, except that the curves appeared to cross at an early time (this may be due to random variations because of very small number of events early on). The figures suggested that the valsartan effects in terms of hazards on the primary adjudicated morbid events and 1st CHF hospitalization appeared to be constant in the most part of study duration.

Table 107.11. Adjudicated Mortality and morbidity endpoints(all randomized patients)

	Valsartan N=2511	Placebo N=2499	Hazard ratio (95% CI)	p-value*
Primary endpoints				
All cause deaths	495 (19.7%)	484 (19.4%)	1.02 (0.90, 1.15)	0.80
Morbid events	723 (28.8%)	801 (32.1%)	0.87 (0.79, 0.97)	0.009
Secondary endpoints				
CV deaths	427 (17.0%)	419 (16.8%)	1.01 (0.89, 1.16)	0.86
Non-fatal morbid events	367 (14.6%)	486 (19.5%)	0.73 (0.64, 0.84)	< 0.0001
Sudden death with Resuscitation	20 (0.8%)	30 (1.2%)	0.66 (0.38, 1.17)	0.15
CHF therapy	7 (0.3%)	8 (0.3%)	0.87 (0.32, 2.40)	0.79
CHF hospitalization	349 (13.9%)	463 (18.5%)	0.73 (0.64, 0.84)	< 0.0001

Source: Reviewers.

Figure 107.2. log(-log(survival)) vs. logarithm of time to primary adjudicated morbid events

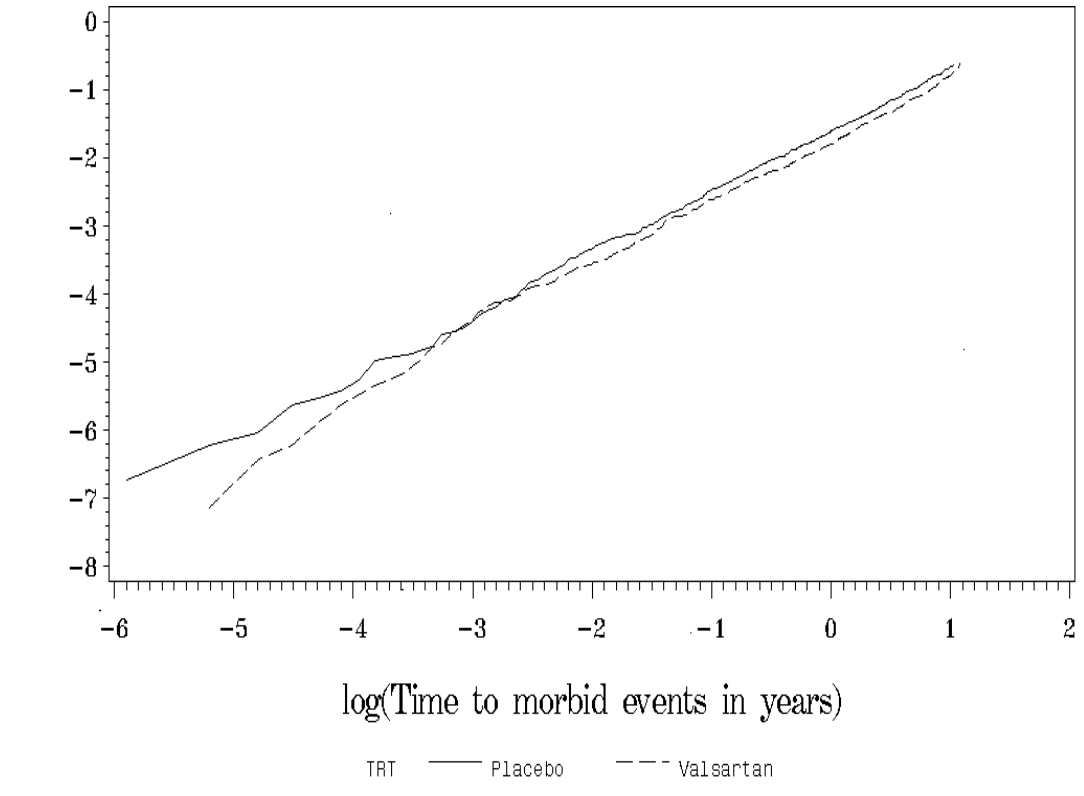
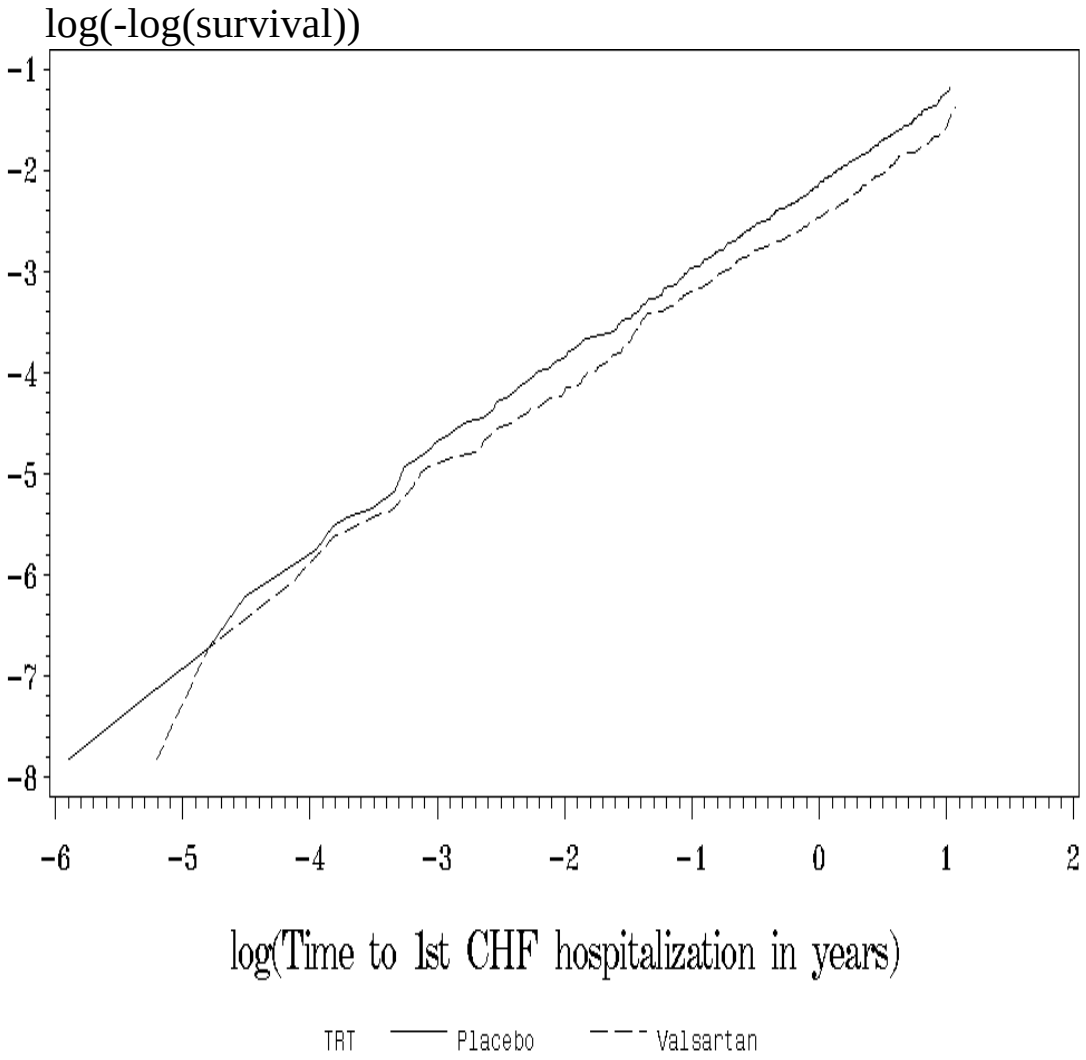


Figure 107.3. log(-log(survival)) vs. logarithm of time to 1st CHF hospitalization



Analysis by censoring those events that occurred after permanent discontinuation of study medication showed the results consistent with the primary analysis (Table 107.12).

Table 107.12. Additional analyses on primary efficacy endpoints

	Valsartan N=2511	Placebo N=2499	Hazard ratio (95% CI)	p-value*
All cause deaths[$]	372 (14.8%)	411 (16.5%)	0.93 (0.81, 1.08)	0.34
Morbid events[$]	585 (23.3%)	720 (28.8%)	0.82 (0.73, 0.91)	0.0003
All cause deaths (until patients last visit)	505 (20.1%)	499 (20.0%)	1.01 (0.89, 1.14)	0.93

[$] Censoring those events that occurred after permanent discontinuation of study medication
Source: Reviewers

At the Agency's request, results were further analyzed for 1. Time to All-cause hospitalization or death; 2. Time to CV-related hospitalization or death; 3. Days Alive and Out of the Hospital. The following analyses were reported:

Table 107.13. Time to death or first hospitalization:

Endpoint*	Valsartan (N=2511)		Placebo (N=2499)		Comparison		
	n	%	n	%	Risk ratio**	95% CI	Log Rank Test p-value
All-cause hospitalization or death	1365	54	1398	56	0.97	(0.90, 1.05)	0.39
CV-related hospitalization or death	1076	43	1145	46	0.91	(0.84, 0.99)	0.02

*cutoff date is May 3, 2000, with non-censoring of events occurring after permanent treatment discontinuation (randomized patients). Time to first hospitalization was based on investigator assessment. **adjusted for NYHA class, LVEF, baseline ACEI category, baseline beta blocker category, etiology, and age group.
Source: Sponsor

Table 107.14. Summary of All-cause Hospitalization Days

All-cause Hospitalizations *	Valsartan (N=2511)		Placebo (N=2499)	
# days alive/out of hospital	Mean 689.5	SD 246.1	Mean 687.7	SD 246.9
# of days in hospital	9.8	22.1	11.0	22.2

*based on investigator assessment. All hospitalizations during the entire core trial were included. Source: Sponsor

In response to further requests from the Agency, the sponsor supplied the following tables for Time to First CHF hospitalization (Endpoint Committee vs. Investigator Assessment), total number of hospitalizations, and frequency distribution of number of patients with hospitalization. The results appear to be consistent with the above findings.

Table 107.15. Analysis results: Time to first CHF hospitalization

Time to First Event	Valsartan N=2511		Placebo N=2499		Comparison (V vs. P)		
CHF Hospitalization	N	%	N	%	Risk Ratio**	95% CI	p-value*
Endpoint Committee***	349	13.9	463	18.5	0.725	(0.631, 0.833)	0.00001
Investigator Assessment***	525	20.9	613	24.5	0.832	(0.740, 0.935)	0.00236

Source: Sponsor. *P-value for both are statistically significant (log rank test). **Cox regression model adjusted for NYHA class, LVEF, baseline ACE categroy, baseline beta blocker category, etiology, age group.
***cut-off date is May 3, 2000 with noncensoring of events occurring after permanent treatment discontinuation (randomized patients).

Table 107.16. Total Number of Hospitalizations (Investigator Assessment)

Cause	Valsartan	Placebo	Difference	Percent difference	p-value*
All-cause	2856	3106	-250	-8.0	0.1445
CHF	923	1189	-266	-22.4	0.0017
Non-CHF	1933	1917	16	0.8	0.8867

Source: Sponsor. *p-value: CMH test for number of hospitalizations stratified for beta blocker (y/n), ACE (y/n) and NYHA (I/II vs. III/IV) as appropriate, using modified Ridit scores.

In an analysis of US vs non-US results, it appears that there is less benefit of valsartan in the US in reducing CHF hospitalization and non-fatal morbid events.

Table 107.17. Mortality and morbidity endpoints (all randomized patients)

	Valsartan	Placebo	Hazard ratio (95% CI)
US	**(N=1093)**	**(N=1085)**	
All cause deaths	227 (20.8%)	222 (20.5%)	1.02 (0.85, 1.22)
Morbid events	350 (32.0%)	375 (34.6%)	0.91 (0.79, 1.06)
CV deaths	191 (17.5%)	185 (17.1%)	1.03 (0.84, 1.26)
Non-fatal morbid events	194 (17.8%)	231 (21.3%)	0.82 (0.68, 1.00)
Sudden death with Resuscitation	12 (1.1%)	13 (1.2%)	0.92 (0.42, 2.01)
CHF therapy	7 (0.6%)	8 (0.7%)	0.87 (0.32, 2.41)
CHF hospitalization	183 (16.4%)	222 (20.5%)	0.81 (0.66, 0.98)
Non-US	**(N=1418)**	**(N=1414)**	
All cause deaths	268 (18.9%)	262 (18.5%)	1.02 (0.86, 1.20)
Morbid events	373 (26.3%)	426 (30.1%)	0.84 (0.73, 0.97)
CV deaths	236 (16.6%)	234 (16.6%)	1.00 (0.84, 1.20)

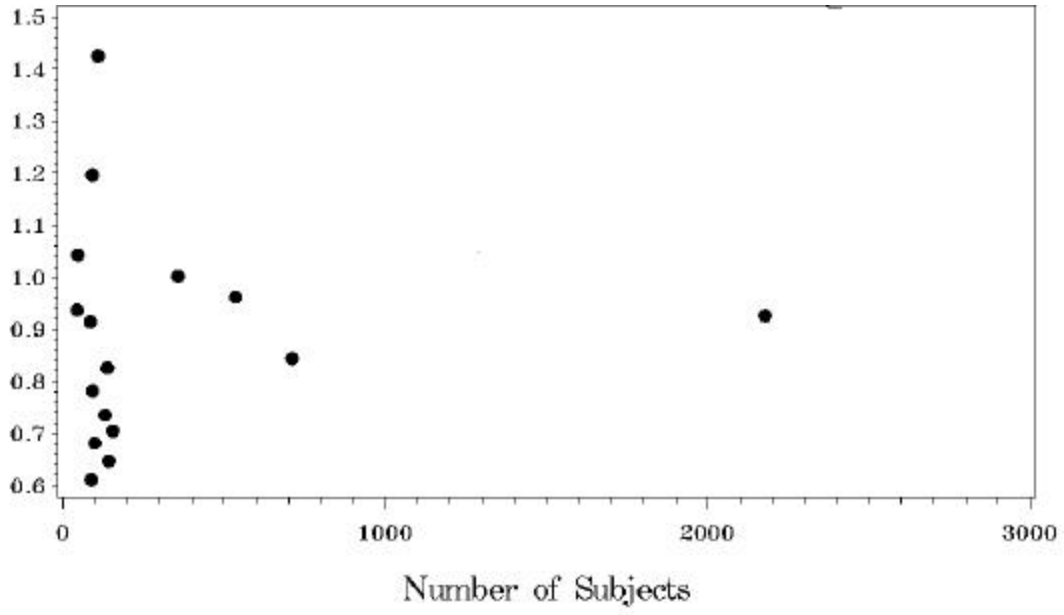
Non-fatal morbid events	173 (12.2%)	255 (18.0%)	0.65 (0.54, 0.79)
Sudden death with Resuscitation	8 (0.6%)	17 (1.2%)	0.47 (0.20, 1.08)
CHF therapy	0	0	----
CHF hospitalization	166 (11.7%)	241 (17.0%)	0.67 (0.55, 0.81)

Source: Reviewers

As illustrated in Figure 107.4, there were no surprising treatment by country interactions on the primary adjudicated morbid events.

Figure 107.4. Relative Risk of Adjudicated Morbid Events by Country

Valsartan/Placebo



The following tables show results of other secondary endpoints. Except for the category, "Third heart sound", most of the signs and symptoms and NYHA category favor valsartan. The results of the change in LV ejection fraction, LHFQ, norepinephrine, and BNP appeared to significantly favor valsartan.

Table107.18. Changes at the last available visit in NYHA class and in clinical signs and symptoms

	Valsartan (N=2511)	Placebo (N=2499)	p-value
NYHA			0.001
Improved	580 (23.1%)	518 (20.7%)	
Worsened	252 (10.0%)	319 (12.8%)	
Paroxysmal nocturnal dyspnea			0.002
Improved	169 (6.7%)	148 (5.9%)	
Worsened	121 (4.8%)	173 (6.9%)	
Dyspnea at rest			0.037
Improved	113 (4.5%)	95 (3.8%)	
Worsened	159 (6.3%)	183 (7.3%)	
Dyspnea on effort			0.003
Improved	858 (34.2%)	791 (31.7%)	
Worsened	470 (18.7%)	528 (21.1%)	
Fatigue			0.010
Improved	795 (31.7%)	736 (29.5%)	
Worsened	539 (21.5%)	628 (25.1%)	
Orthopnea			0.20
Improved	358 (14.3%)	348 (13.9%)	
Worsened	265 (10.6%)	286 (11.4%)	
Jugular venous distension			0.001
Improved	204 (8.1%)	195 (7.8%)	
Worsened	137 (5.5%)	179 (7.2%)	
Edema			0.003
Improved	299 (11.9%)	247 (9.9%)	
Worsened	253 (10.1%)	305 (12.2%)	
Rales			0.001
Improved	181 (7.2%)	166 (6.6%)	
Worsened	152 (6.1%)	206 (8.2%)	
Third heart sound			0.22
Improved	337 (13.4%)	303 (12.1%)	
Worsened	139 (5.5%)	139 (5.6%)	

Source: Reviewers

LHFQ was assessed only in patients in the USA, UK, Australia and Italy (specific countries were not prespecified in the protocol or amendments). The LHFQ sample size was 1587 for valsartan and 1573 for placebo; missing values were < 5%.

Table 107.19. Change at last available visit in secondary efficacy parameters

	Valsartan		Placebo		V minus P (95% CI)	p-value
	N	Δ	N	Δ		
LVEF (%)	2300	4.37	2336	3.57	0.80 (0.31, 1.29)	0.0014
LVIDD/BSA (cm/m2)	2294	-0.09	2331	-0.04	-0.05 (-0.07, -0.03)	< 0.0001

LHFQ score – Overall	1508	1.46	1512	3.26	-1.80 (-3.02, -0.58)	0.004
LHFQ score – Physical	1507	0.79	1511	1.55	-0.77 (-1.34, -0.19)	0.009
LHFQ score – Emotional	1505	0.16	1512	0.55	-0.39 (-0.75, -0.04)	0.029
Norepinephrine (pg/mL)	1951	-8.08	1987	20.62	-28.7 (-44.9, -12.5)	0.0005
Brain natriuretic peptide (pg/mL)	1950	-18.97	1987	25.61	-44.6 (-57.2, -32.0)	< 0.0001

Source: Reviewers

An analysis of morbid and mortal events by subgroup is presented below. No subgroup showed (very) inconsistent results. The valsartan appeared to have little favorable, or even adverse effect on morbid events in the patients who receiving ACE inhibitors or beta blockers or both, compared to the patients who did not receive either.

Table 107.20. Adjudicated Morbidity endpoint in subgroups (all randomized patients)

	Valsartan (N=2511)	Placebo (N=2499)	Hazard ratio (95% CI)
Age			
< 65	330 (24.1%)	348 (26.9%)	0.88 (0.76, 1.02)
≥ 65	393 (34.4%)	453 (37.6%)	0.88 (0.77, 1.01)
Gender			
Male	590 (29.4%)	641 (32.1%)	0.90 (0.80, 1.00)
Female	133 (26.4%)	160 (32.1%)	0.79 (0.63, 0.99)
Race			
Caucasian	635 (28.2%)	715 (31.5%)	0.87 (0.78, 0.97)
Black	68 (37.4%)	52 (32.1%)	1.21 (0.84, 1.74)
Oriental/Other	20 (27.0%)	34 (51.5%)	0.44 (0.26, 0.77)
NYHA Class			
I	0	0	--
II	350 (22.4%)	378 (24.6%)	0.91 (0.78, 1.05)
III	347 (38.3%)	387 (42.7%)	0.85 (0.73, 0.98)
IV	26 (61.9%)	36 (65.5%)	0.81 (0.49, 1.35)
LVEF			
< baseline median	400 (33.0%)	449 (38.2%)	0.83 (0.72, 0.95)
≥ baseline median	323 (24.9%)	352 (26.6%)	0.92 (0.79, 1.07)
CHF etiology			
Ischemic	471 (32.6%)	476 (33.5%)	0.96 (0.84, 1.08)
Non-ischemic	252 (23.7%)	325 (30.1%)	0.76 (0.64, 0.89)
ACEI use			
No	46 (24.9%)	77 (42.5%)	0.51 (0.35, 0.73)
Yes	677 (29.1%)	724 (31.2%)	0.92 (0.82, 1.02)
Beta-blocker use			
No	506 (30.8%)	599 (37.1%)	0.80 (0.71, 0.90)
Yes	217 (25.0%)	202 (22.9%)	1.10 (0.91, 1.33)

ACE=no/beta=no	31 (27.6%)	54 (47.4%)	0.52 (0.34, 0.81)
ACE=yes/beta=no	475 (31.0%)	545 (36.3%)	0.82 (0.73, 0.93)
ACE=no/beta=yes	15 (20.5%)	23 (34.3%)	0.51 (0.26, 0.97)
ACE=yes/beta=yes	202 (25.4%)	179 (21.9%)	1.18 (0.97, 1.45)

Source: Reviewers

Table 107.21. All-Cause mortality endpoint in subgroups (all randomized patients)

	Valsartan (N=2511)	Placebo (N=2499)	Hazard ratio (95% CI)
Age			
< 65	208 (15.2%)	194 (15.0%)	1.02 (0.84, 1.24)
≥ 65	287 (25.1%)	290 (24.0%)	1.04 (0.88, 1.22)
Gender			
Male	415 (20.7%)	401 (20.1%)	1.04 (0.90, 1.19)
Female	80 (15.9%)	83 (16.6%)	0.93 (0.68, 1.27)
Race			
Caucasian	444 (19.7%)	444 (19.6%)	1.00 (0.88, 1.15)
Black	37 (20.3%)	23 (14.2%)	1.50 (0.89, 2.52)
Oriental/Other	14 (18.9%)	17 (25.8%)	0.72 (0.36, 1.46)
NYHA Class			
I	0	0	--
II	242 (15.5%)	222 (14.5%)	1.09 (0.91, 1.31)
III	233 (25.7%)	238 (26.3%)	0.95 (0.79, 1.14)
IV	20 (47.6%)	24 (43.6%)	1.04 (0.58, 1.89)
LVEF			
< baseline median	267 (22.0%)	286 (24.4%)	0.90 (0.76, 1.06)
≥ baseline median	228 (17.6%)	198 (14.9%)	1.18 (0.98, 1.43)
CHF etiology			
Ischemic	339 (23.4%)	304 (21.4%)	1.10 (0.94, 1.28)
Non-ischemic	156 (14.6%)	180 (16.7%)	0.87 (0.70, 1.08)
ACEI use			
No	32 (17.3%)	49 (27.1%)	0.59 (0.37, 0.91)
Yes	463 (19.9%)	435 (18.8%)	1.07 (0.93, 1.21)
Beta-blocker use			
No	353 (21.5%)	374 (23.1%)	0.92 (0.79, 1.06)
Yes	142 (16.4%)	110 (12.5%)	1.35 (1.05, 1.73)
ACE=no/beta=no	19 (17.0%)	36 (31.6%)	0.50 (0.28, 0.86)
ACE=yes/beta=no	334 (21.8%)	338 (22.5%)	0.96 (0.82, 1.11)
ACE=no/beta=yes	13 (17.8%)	13 (19.4%)	0.80 (0.37, 1.74)
ACE=yes/beta=yes	129 (16.2%)	97 (11.9%)	1.42 (1.09, 1.85)

Source: Reviewers

Safety:
Safety results are presented below and in the Integrated Summary of Safety.

Table 107.22. Number (%) of patients with adverse experience by Treatment group (Safety analyzable patients) with incidence > 1.0% and greater than Placebo (in descending order for Valsartan)

Adverse Experience—Primary Term	Valsartan (N=2506)		Placebo (N=2494)	
Patients with an adverse experience	2295	91.6	2235	89.6
Dizziness (exc vertigo)**	627	25.0	451	18.1
Hypotension NOS*	347	13.9	201	8.1
Nasopharyngitis	250	10.0	229	9.2
Diarrhea NOS**	238	9.5	193	7.7
Arthralgia**	195	7.8	172	6.9
Influenza	184	7.3	173	6.9
Hyperkalemia¶	163	6.5	81	3.3
Limb pain	154	6.2	146	5.9
Back pain***	145	5.8	122	4.9
Renal impairment NOS	135	5.4	76	3.1
Ventricular tachycardia	125	5.0	119	4.8
Gout	125	5.0	113	4.5
Anemia NOS	119	4.8	110	4.4
Fatigue*	117	4.7	106	4.2
Postural hypotension	95	3.8	48	1.9
Dizziness postural	92	3.7	54	2.2
Myocardial Infarction	89	3.6	78	3.1
Dehydration	84	3.4	65	2.6
Dyspepsia***	79	3.2	78	3.1
Vertigo NEC***	78	3.1	51	2.0
Hyperglycemia NOS	62	2.5	55	2.2
Pruritis NOS***	59	2.4	57	2.3
Paresthesia NEC***	55	2.2	41	1.6
Renal failure NOS[@]	54	2.2	31	1.2
Vision blurred	55	2.2	22	0.9
Blood creatinine increased	54	2.2	27	1.1
Weight increased	45	1.8	38	1.5
Anorexia	45	1.8	39	1.6
Renal failure acute	46	1.8	43	1.7
Gastroenteritis NOS	43	1.7	25	1.0
Hyperlipidemia NOS	42	1.7	29	1.2
Ventricular fibrillation	39	1.6	37	1.5
Arrhythmia NOS	39	1.6	31	1.2
Neck pain	38	1.5	35	1.4
Intermittent claudication	35	1.4	19	0.8
Digoxin toxicity	35	1.4	30	1.2
Inguinal hernia NOS	33	1.3	26	1.0
Abdominal distension	33	1.3	29	1.2
Diabetes mellitus aggravated	29	1.2	18	0.7
Nasal congestion	30	1.2	28	1.1
Hypothyroidism	27	1.1	24	1.0
Ventricular extrasystoles	27	1.1	22	0.9
Herpes zoster	27	1.1	22	0.9

Infection NOS	28	1.1	20	0.8
Hyperuricemia	27	1.1	18	0.7
Contusion	27	1.1	26	1.0
Wheezing	26	1.0	13	0.5

Safety analyzable= patients who received drug and for whom safety data are available.
Source: Volume 29: Table 10.1-1
*Noted in current Valsartan (Diovan) labeling: Hypotension in Volume and/or Salt-Depleted Patients is listed under Warnings. Fatigue is listed as having occurred in at least 1% of patients and at a higher incidence than placebo (Placebo-controlled clinical trials).
**Noted in current Valsartan labeling: listed as having occurred in more than 1% of patients but at about the same incidence in placebo and valsartan patients.
***Noted in current Valsartan labeling: listed as an adverse experience that occurred in >0.2% of valsartan patients, without determination of causality.
¶Noted in labeling under Clinical Laboratory Test Findings and Post-Marketing experience.
@Noted in labeling under Post-Marketing Experience.

Table 107.23. Serious Adverse Experiences by Primary term (incidence > 1.0% for Valsartan and occurring at higher rate than placebo) (Safety Analyzable)

	Valsartan (N=2506)		Placebo (N=2494)	
Patients with a serious adverse experience	N 1282	% 51.2	N 1342	% 53.8
Angina pectoris	63	2.5	49	2.0
Myocardial infarction	83	3.3	73	2.9
Ventricular tachycardia	84	3.4	77	3.1
Dehydration	49	2.0	33	1.3
Hyperkalemia	40	1.6	23	0.9
Dizziness (exc. Vertigo)	39	1.6	36	1.4
Syncope	62	2.5	60	2.4
Renal impairment	44	1.8	20	0.8
Renal failure acute	30	1.2	27	1.1
Renal failure NOS	25	1.0	15	0.6
Hypotension NOS	55	2.2	48	1.9

Source: Volume 35: Table 10.2-3

Table 107.24. Adverse Experiences Leading to Study Discontinuation (Incidence > 1.0% in Valsartan and Greater than placebo) (Safety analyzable population)

	Valsartan (N=2506)	Placebo (N=2494)
	n (%)	n (%)
Patients with an adverse experience	249 (9.9)	181 (7.3)
Dizziness (exc vertigo)	41 (1.6)	11 (0.4)
Hypotension NOS	32 (1.3)	20 (0.8)
Renal impairment NOS	27 (1.1)	6 (0.2)

Source: Volume 35, Table 10.2-5a

107. 25. Abnormal Laboratory Values reported as AE and leading to treatment discontinuation (Incidence > placebo) (Safety analyzable population)

	Valsartan (N=2506)	Placebo (N=2494)
	n (%)	n (%)
Number of patients with lab AE leading to treatment discontinuation	31 (1.2)	9 (0.4)
Blood creatinine increased	13 (0.5)	3 (0.1)
Hyperkalemia	13 (0.5)	2 (0.1)
Hyperbilirubinemia	1 (0.04)	0
Hypokalemia	1 (0.04)	0
Thrombocytopenia	1 (0.04)	0
Anemia NOS	3 (0.1)	1 (0.04)

Source: Volume 35, Table 10.2-7

Table 107.26. Mean (± SD) Sitting Pulse, Systolic and Diastolic Blood Pressure, and Body Weight Changes by Treatment Group (Safety Analyzable population)

	Valsartan			Placebo		
	N**	Baseline	Change from baseline to endpoint*	N**	Baseline	Change from baseline to endpoint*
Sitting SBP (mm Hg)	2494	123 (18)	-7 (18)	2482	124	-4 (18)
Sitting DBP (mm Hg)	2494	76 (11)	-5 (11)	2482	76 (11)	-3 (11)
Sitting pulse (bpm)	2493	73 (13)	-0.5 (13)	2481	74 (13)	-0.3 (13)
Body weight (kg)	2491	80 (16)	0.6	2480	79 (15)	-0.1 (6)

*Endpoint=last observation post-baseline

** =Patients with both baseline and postbaseline observation for that visit except month 0.

Source: Volume 35, Table 10.4-1.

Results for standing vital signs were similar to these values.

Reviewer's Comments:

1. There was no survival benefit demonstrated for valsartan.
2. A benefit was demonstrated for valsartan in: prolonging time to first CHF hospitalization, signs and symptoms of CHF, change in EF and LVIDD, LHFQ, and neurohormones.
3. Valsartan did not appear to prolong the time to first all-cause hospitalization.
4. Valsartan was associated with an increased treatment-emergent adverse events as well as an increased AE-related discontinuation rate. Dizziness, hypotension, hyperkalemia, diarrhea and renal impairment occurred more frequently in the valsartan group compared to placebo.
5. Explaining the different results of "time to first CHF hospitalization" vs. "time to first 'all-cause' hospitalization" remains an outstanding issue. At least two possible explanations exist: 1. A bias in the adjudication process; 2. No bias in the adjudication process--Valsartan may prolong the time to first CHF hospitalization, but this benefit is "offset" by increased drug (valsartan)-related hospitalizations. Pending requests have been made to the sponsor to explore both possibilities. These include: a detailed explanation of adjudication procedure,

the lists of non-CV first hospitalizations and narratives supplied to the adjudication committee, an analysis of renal failure patients as well as those requiring dialysis by treatment group.

Study 107 (Substudy 02): Multi-country, randomized, double-blind, placebo controlled trial to assess the effect of valsartan on morbidity and mortality, signs and symptoms, and quality of life in patients with stable, chronic congestive heart failure (NYHA Class II-IV): Six-Minute Walk Substudy. (Phase III) (Protocol date: June 9, 1997)

Source: NDA Volume 64 (Protocol, Case Report Form, Study Report); electronic database

Primary Objective:

- Assess the effect of valsartan, compared to placebo, on exercise capacity as measured by the distance walked in a six-minute walk test in patients with stable, chronic congestive heart failure (NYHA Class II-IV) 4 months following randomization into valsartan Protocol 107.

Secondary Objective:

- Assess the relationship of distance walked at baseline with mortality and morbidity endpoints.

Sites: 67 sites in 11 countries; 28 sites in the USA.

Duration: August 8, 1997 (first patient, first visit) to August 17, 1999 (last patient, last visit)

Study Design:
This was a substudy of patients enrolled in valsartan Protocol 107. Selected trial sites would utilize the same trial design, randomization, control/comparator, dosing, blinding, inclusion/exclusion criteria as in Study 107. In this substudy, the six-minute walk test was to be performed at Visits 1, 2, 6 and 7 after all other visit procedures in Study 107 were completed (see Study 107 for Visit schedule). Symptoms experienced by patients during the walk were to be recorded on the "Adverse Experience During Six-Minute Walk test" case report form. In addition, at Visits 3, 4, 5, 8, and 9, any continuing adverse experiences that began and did not resolve during the previous six-minute walk test were to be recorded on the "Adverse Experience During Six-Minute Walk Test" case report form provided at each of these visits.
Six-minute walk tests were to be performed up to month 4 (Visit 7), with safety follow-up to month 9 (Visit 9; see Study 107).

Six-Minute Walk Test:
As prespecified in the protocol, the six-minute walk test consisted of a measured 20 meter distance in a level enclosed corridor, marked with a chair at either end. The patient was instructed to walk from end to end at their own pace while attempting to cover as much ground as possible in the allotted 6 minute time period. A supervisor was to call out the time every 2 minutes and encourage the patient every 30 seconds in a standardized fashion, face the patient and deliver one of two phrases ("you're doing well"; "keep up the good work"). Patients were allowed to stop and rest during the test but were to be instructed to resume walking as soon as they were able. After 6 minutes, patients were instructed to stop walking; total distance (to the nearest half meter) was to be measured and symptoms experienced by the patient were to be recorded.

Removal of patients from substudy:
In addition to prespecified events in Study 107, patients were to be removed from the Substudy if they were no longer ambulatory (e.g., broken leg).

Sample Size Determination:
A total of 508 patients, 254 per treatment group, who met all admission/randomization criteria and completed all 6-minute walk tests was needed to detect a treatment difference of 30 meters in 6-minute walking distance with 80% power at a 5% significance level, assuming a standard deviation of 120 meters. It was anticipated that approximately 706 patients were to be enrolled into this substudy in order to meet the required size of 508 completed patients.

Randomization:
As part of the Val-heft study, patients were stratified, at randomization, according to their use of beta blockers (yes/no). Please see Study 107 for further details.

Statistics:
The primary efficacy variable was the change from baseline in 6-minute walking distance. The baseline value used for 6-minute walking distance was the pre-randomization walking distance measurement at Visit 2.
The criterion for efficacy was a statistically significant difference with respect to the primary variable, favoring valsartan (plus background) over placebo (plus background).
The primary analysis was the intent-to-treat analysis of the primary efficacy variable at Endpoint. In addition, all variables were to be analyzed separately at each scheduled measurement time point, based on all randomized patients with baseline and post-baseline evaluations at the corresponding timepoint.
Between-treatment comparisons of valsartan versus placebo were based on the null hypothesis of no treatment difference. All tests were based on two-sided alternative hypotheses. All tests were made at the 5% (0.05) significance level.
A two-factor analysis of covariance was to be performed for the change from baseline in 6-minute walking distance, with center and treatment group as factors and baseline walking distance, baseline ACEI category (y/n), and baseline beta blocker category (y/n) as covariates. Missing walking distance measurements during the double-blind period, because of an inability to walk due to severity of CHF or death, were given a value of zero. Otherwise, no value substitution was made for the missing measurement. After substitution for missing values, the last value was to be the last value carried forward for the terminal visit analysis.

A nonparametric analysis of walking distance ranks was to be performed for robustness purposes. In addition, pooling criteria was prespecified in the protocol.

Safety Variables: As noted above, all new or continuing adverse experiences were to be recorded, as well as any exercise-related adverse experiences.

Amendments to the Protocol: See Study 107 for five amendments to the protocol. There were no amendments specific to Substudy 02.

Results:
Patient Disposition:

According to the electronic database and the study report, 751 patients were enrolled and 71 patients were discontinued prior to randomization. Of those randomized, about 38-39% of patients were from the US, followed by 15-16% from Italy and about 11% from the Netherlands; there were no meaningful differences between the two treatment groups. (Source: walkenr.xpt and vwalk.xpt).

Table 107.27. Patient Disposition

	Valsartan n (%)	Placebo n (%)	Total n (%)
Enrolled	--	--	751
Randomized	349 (100)	333 (100)	682 (100)
Permanently discontinued trial treatment prior to Visit 7	23 (7)	8 (2)	31 (5)
Completed (to death or study end)	320 (92)	304(91)	624 (91)
Premature substudy termination*	29 (8)	29(9)	58 (9)
Inability to walk (possible CHF-related)	1(.3)	0	1(.1)
Inability to walk (not CHF-related)	3 (1)	1(.3)	4 (1)
Missing values	25 (7)	28 (8)	53 (8)

Source: electronic database (walkenr.xpt, walk.xpt, walkdisc.xpt) and Table 7.1-2 (Volume 64)
*Not completing 4 month substudy and no death

Table 107.28. Analysis Sets

	Valsartan	Placebo
Intent to treat (ITT)	349	333
Clinically assessable (CAP)	333	326
Safety analyzable (SAP)	347	333

Source: electronic database (walkana.xpt)

Table 107.29. Baseline Characteristics:

	Valsartan (N= 349) n (%)	Placebo (N=333) n (%)
Male (%)	278 (80)	256 (77)
Race: Caucasian	307 (88)	299 (90)
Black	36 (10)	28 (8)
Oriental/other	6 (2)	6 (2)
Age < 65 years	186 (53)	182 (55)
Age ≥ 65 years	163 (47)	151 (45)
NYHA Class I	1 (0.3)	0
II	223 (64)	209 (63)
III	116 (33)	117 (35)
IV	9 (3)	7 (2)
Etiology: Coronary disease	183 (52)	191 (57)
Idiopathic cardiomyopathy	121 (35)	101 (30)
Hypertension	21 (6)	23 (7)

Other	24 (7)	18 (5)
Use of CHF-related medications		
ACE inhibitors	327 (94)	313 (94)
Diuretics	307 (88)	291 (87)
Digoxin	232 (67)	225 (68)
Nitrates (short and long-acting)	149 (43)	145 (44)
Beta-blockers	130 (37)	118 (36)
Calcium channel blockers	47 (14)	44 (13)
Antiarrhythmics	40 (12)	36 (11)
Mean (± SD)		
Age (yrs)	62 (11) Range: 21-96	62 (11) Range: 28-87
Height (cm)	170 (9) Range: 141-191	170 (10) Range: 128-198
Weight (kg)	79 (15) Range: 41-131	78 (15) Range: 40-139
CHF Duration (mos)	46 (47) Range: 3-276	51 (54) Range: 2-340

Source: electronic database (walkdeba.xpt, walkdemo.xpt, walkbase.xpt)

Table 107.30. Baseline walk test

	Valsartan (N=347)	Placebo (N=333)
Mean (± SD) baseline walking distance Range	372 (114) 15-780	367 (117) 22-750
Terminated walk test < 6 min	13	18
Reason for termination of walk test		
Dyspnea	9	9
Fatigue	2	6
Angina	1	0
Other	1	3

Source: electronic database (walkeff.xpt) Under the category "patient able to walk" 2 patients (from the total N of 349 in the valsartan group) were listed as "unknown" (listed as not related to CHF) and 347 were listed as "able to walk".

Table 107.31. Drug Exposure:

	Valsartan (N=349)	Placebo (N=333)
N	343	331
Mean (± SD) duration of exposure to study medication (days)	109 (34)	114 (30)
Range	1-201	1-219
Mean (± SD) daily dose (mg)	225 (72)	249 (52)
Range	80-289	80-285

Source: Volume 64: Table 8.1-1. Mean daily dose was calculated as: [(number of days on level 1 x 80) + (number of days on level 2 x 160) + (number of days on level 3 x 320)]/ number of days on trial medication.

Table 107.32. Primary Efficacy results (all randomized patients):

		Raw Means (m)		Change	LS Mean Change	Difference in LSM change	CI	P value
	N*	Baseline	Endpoint					
Valsartan	320	372.7	385.3	12.6	14.91	1.18	(-11.2, 13.6)	0.85
Placebo	313	373.6	384.8	11.2	13.73			

Source: Volume 64: Table 9.1-1a ANOVA results controlling for pooled center, baseline value, baseline ACEI category, baseline Beta B category and treatment by baseline value interaction.
*N is the number of patients with observations at both baseline and endpoint. Endpoint is the last available post-baseline observation (LOCF).

Primary Efficacy results are presented above. Improvements in walking distance were seen in both treatment groups; there was no significant difference seen between the two treatment groups. In addition, the number and percent of patients terminating the walk test prior to 6 minutes was similar between the two treatment groups (9 valsartan and 11 placebo patients at month 2; 8 valsartan and 8 placebo patients at month 4; and 8 valsartan and 9 placebo patients at endpoint, respectively). The most common reason for test termination was dyspnea.

A subgroup analysis (below) was submitted by the sponsor. Patients on placebo who were not on a background ACE inhibitor showed a worsening in walking distance compared to baseline; the other groups showed improvements of varying degrees. The differences in baseline walk distances (as in ACEI use, age, gender, LVEF, and LWFQ categories) and differences in sample size (e.g. categories of ACEI use and race) will affect comparisons by and within a subgroup.

Table 107.33. Subgroup analysis: Change from baseline to endpoint in walking distance by subgroup

		Valsartan			Placebo		
Parameter		N*	Mean Baseline	Change**	N*	Mean Baseline	Change**
ACEI	Yes	302	375	11	296	378	14
	No	18	335	38	17	306	-37
Beta blocker	Yes	122	384	16	110	388	14
	No	198	366	11	203	366	10
Age	<65	177	396	12	175	395	17
	≥ 65	143	344	13	138	347	4
Gender	Male	253	383	11	242	388	8
	Female	67	333	18	71	323	23
Race	White	282	372	13	281	370	8
	Black	33	376	6	27	418	35
	Oriental/other	5	369	21	5	329	62

LVEF baseline	< median	125	382	8	113	369	1
	≥ median	195	366	16	200	376	17
Overall LWHF score	< median	99	384	13	94	396	6
	≥ median	95	341	10	96	324	4

Source: Sponsor: Table 9-2, 9-3 (Study Report); table 9.1-2, 9.2-3, 9.2-4
N*=non-missing at Endpoint
**Change from baseline to Endpoint. Endpoint is last observation post baseline.

Secondary Efficacy Variable:
Since the primary efficacy endpoint was not met, a correlation with morbid/mortal endpoints was not performed.

Safety:

Deaths: There were no deaths during the six-minute walk test. A total of 24 patients randomized into the substudy died during the duration of this study. Please see Study 107 and the Integrated Summary of Safety for further discussion of deaths.

Table 107.34. Serious adverse experiences during the walk test:

Treatment	Patient #	Event	Severity	Onset	Duration study drug	Fatal
Valsartan	17/14159	Ventricular flutter	Severe	Day 57	779	No
Placebo	23/1965	Dyspnea	Mild	Day 1	27 days	No
Placebo	11/10118	Intermittent claudication	Moderate	Day 1	13 days	no

Source: Table 10-5. Study Report

Other safety evaluations: For further discussion, including evaluation of laboratory results, please see the Integrated Summary of Safety.

Summary:
This was a four month, 682 patient, 67 site substudy of the Val-heft trial evaluating the effect of background CHF therapy plus valsartan compared to placebo, on the six-minute walk test in patients with chronic stable Class II-IV CHF.

Conclusions:
1. Improvements were seen in 6 minute walk test in both placebo and valsartan groups.
2. There was no significant difference in six-minute walk test between the two treatment groups.

Study 110. A twelve week, multicenter, randomized, double-blind, active-controlled study to assess the efficacy and safety of valsaertan compared to enalapril on exercise capacity in patient s with stable, moderate, chronic heart failure

Table of Contents Study CVAL4890110
Division of Cardio-Renal Drug Products
Medical Officer Review

Study # CVAL4890110 (abbreviated here as study 110)

Title of study: A twelve week, multicenter, randomized, double-blind, active-controlled study to assess the efficacy and safety of valsartan compared to enalapril on exercise capacity in patients with stable, moderate, chronic heart failure (NYHA II-III)

Investigator and sites: A total of 15 sites were planned, 13 of these sites enrolled subjects. The investigators and sites are shown in table 110.1.

Table 110.1 Investigator and sites:

Center 001 Dr. K. Salden Sahlgren's Hospital, Gothenberg University Gothenburg, Sweden	Center 002 Dr. R. Willenheimer Malmo University Hospital Malmo, Sweden	Center 003 Dr. T. Wallen Vasa Hospital, Gothenburg University Gothenburg, Sweden	Center 004 Dr.K. Schenck-Gustafsson Karolinska Hospital, Karolinska Institute Stockholm, Sweden
Center 005 Dr P. Lofdahl Hjart-mattagningen Helsingborg, Sweden	Center 006 Dr. U. Dalstrom Linkoping university Hosptital Linkoping Sweden	Center 007 Dr. E. Panlev Lund University Hospital Lund, Sweden	Center 008 Dr. M. Freitag Blekinge Hospital Karolinska. Sweden
Center 009 Prof Ch. Sylven Huddinge Sjukhus Huddinge, Sweden	Center 010 Dr F. Huhtasaari Subderbyn Hospital Lulea, Sweden	Center 011 Dr. T. Tygesesn Boras Hospital Boras, Sweden	Center 012 Dr. M. Edner Danderyd Hospital Karolilsnska Institute Stolkholm, Sweden
	Center 013 B. Friberg Ostersund Hospital Ostersund, Sweden		

Formulations: Formulations are shown in Table 110.2

Table 110.2 Formulations used in study CVAL4890110

Valsartan 80 mg Valsartan 160 mg Valsartan Placebo	B980164, B970033 B980068, B980168 B980004, B980008
Enalapril 5mg Enalapril 10 mg Enalapril Placebo	B980228 B980229 B980027

Dates of study:

Protocol Dated: 21 April 1999
Protocol Amendment 21 June 1999
First Patient enrolled 31 August 1999
Last patients entered 31 January 2000
Statistical Submission: 20 December 2000
Blind Broken. Not stated.

The statistical report as written after the last patient completed the study. The date at which blind was broken is unclear.

Primary end point: The primary end point of the study was the six-minute walk distance. The primary population of interest was defined as the "Full Set Analysis" population. This population had both baseline and at least one-post baseline measurement. In addition, the population was to satisfy three major enrollment criteria:

1. NYHA Class II/III at visit 1 (baseline).
2. Resting left ventricular ejection fraction at visit 1 $\leq$ 45%.
3. On ACE inhibitor treatment for at least 3 months prior to randomization.

Subsequently, upon submission of the statistical report (dated 20 December 2000), the sponsor defined the imputation of a "0" walk distance for those unable to walk because of severe CHF or if they were dead. The statistical report was dated well after all patients should have completed the 12-week study (estimated as May 1, 2000).

The primary analysis was an ANCOVA with center and treatment as factors and baseline walking distance as covariate. Treatment by baseline walking distance was also included in the model. A further model with terms for center, baseline walking distance, treatment and baseline interaction, and center by treatment interaction was also assessed. If the interaction term was significant at the 10% level, treatment differences within centers were investigated.

The sponsor analyzed the data first to determine "non-inferiority", which they defined as demonstrating that the lower bound of walking distance was no worse than 45 meters less than enalapril. If the analysis did not violate the 45-meter worsening, a comparison against enalapril for superiority will be performed.

[Comment: No rationale is defined for indicating why 45 meters in a six-minute constitutes a reasonable bound for non-inferiority. This reviewer knows of no placebo-controlled study that shows an increase in this metric by 90 meters (at the lower confidence interval bound), so that a 45-meter non-inferiority claim would be credible. In fact this reviewer knows of no placebo-controlled studies against ACE-inhibitors that were successful in demonstrating a 6-minute walk benefit of any magnitude for the ACE-inhibitor. The non-inferiority claim, therefore appears to be capricious.]

Secondary efficacy end points: The four secondary efficacy end points are described below. Each of these end points was analyzed by an ANCOVA with center and treatment as factors and baseline measurement as covariate. Two-sided 95% confidence intervals of Valsartan value – Enalapril value (baseline corrected) were tabulated.

1) The dyspnea fatigue index.

This index consists of measurements that relate to the magnitude of task, the magnitude of pace and the functional impairment. The higher the value the less symptomatic the patient. The specifics of the scale is shown below

Table 110.3 Components and specific characterization of the Dyspnea-Fatigue Index.

Value	Magnitude of Task (at normal pace)	Magnitude of Pace	Functional impairment
4	'Extraordinary". Becomes short of breath or fatigued only with extraordinary activity such as carrying heavy loads on level ground, lighter loads uphill or running. No symptoms with ordinary tasks.	"Extraordinary". Essentially all conceivable physical tasks are performed at normal pace.	"None". Can carry out usual activities and occupation (if employed before onset of congestive heart failure) without symptoms.
3	"Major". Becomes symptomatic only with such major activities as walking up a steep hill, climbing more than 3 flights of stairs or carrying a moderate load on the level	"Major". Major tasks, as defined earlier, are performed at a reduced pace, taking longer to complete. Less strenuous tasks can be done at normal pace.	"Slight". Distinct impairment in at least 1 activity but no activities completely abandoned. A change in activity may have occurred at work or in other activities, but change is slight and is not clearly caused by shortness of breath or fatigue.
2	"Moderate". Becomes symptomatic with moderate or average tasks such as walking up a gradual hill, climbing less than 3 flights of stairs or carrying a light load on level ground	"Moderate". Moderate tasks, as defined earlier, are performed at a reduced pace, taking longer to complete. Light tasks can be done at normal pace	"Moderate". Patient has changed jobs or has abandoned at least given up most or all usual activities.
1	"Light". Becomes symptomatic with light activities, such as walking on the level, washing or standing	"Light". Light tasks are done at a reduced pace.	"Severe". Patient is unable to work or has given up most or all usual activities.
0	"None". symptomatic at rest, while sitting or lying down.	"None". Symptomatic at rest.	"Very Severe". Unable to work and has given up most or all usual activities.

2) Living with heart failure questionnaire:

This questionnaire consisted of 21 questions with value of 0-5. The questions reflect the clinical impairment of heart failure as perceived by the subject. A value of "0" reflect little impairment, a value of "5" reflect substantial impairment. A decrease in the metric reflects improvement.

If < 25% of the values of an individuals assessment were missing, the average value of the reported questions was extrapolated to the questionnaire as a whole. If > 25% of the values were missing, the questionnaire value for that visit was excluded.

3) Atrio-ventricular plane displacement: This is an echocardiographic measurement that reflects the excursion of the A-V plane between the position most remote from the apex. The average of measurements taken in the anterior, lateral, posterior and anterior regions was used as the metric for patients with regular rhythm. For those who had irregular rhythms, eight measurements were taken.

4) Left ventricular end diastolic diameter. This measurement is also an echocardiographic measurement.

Inclusion criteria:

- Patients > 18 years old with stable, moderate chronic heart failure (NYHA II-III) diagnosed at least 3 –months prior to the baseline visit (visit 1). Patients were to be on ACE-inhibitors for at least 3 months.
- An EF $\leq$ 45% by echocardiography.

- Stable course and stable medication during the two weeks prior to the enrollment visit (week1).
- Exercise capacity solely limited by CHF.
- Can sign informed consent.

Exclusion criteria:

- Patients with complicated disease including right heart failure due to pulmonary disease, clinically significant valvular lesions or outflow obstruction, infective cardiomyopathy or active peri- or myocarditis.
- Rapidly deteriorating or uncompensated heart failure.
- Recent cardiovascular insult such as MI, cardiac surgery, unstable angina, exercise-induced angina, VT or other arrhythmia, within 3 months of entry or a PTCA within 6 months of entry.
- CAD likely to need intervention during the study period.
- Persistent standing SBP < 90 mm Hg.
- Abnormal serum creatinine (>200 umol/l) and AST (> 3 x upper limit of normal.
- Exercise limited for reasons other than CHF.
- Contraindication to ACE inhibitors of angiotensin II blockers.
- Treatment with angiotensin blockers in the three months prior to visit 1 or during the study.
- Recent (within 30 days) use of investigational new drugs.
- Previous participation in Valsartan CHF trials.
- Other condition that might interfere with efficacy or safety assessment.

Protocol: Subjects were initially enrolled in a 2-week single blind placebo run in period during which they remained on open-labeled ACE- inhibitor. At the end of this period the specific ACE-inhibitor was discontinued and subjects were started on double-blinded medication, either enalapril or valsartan. The specific procedures and timing are shown in table 110.4.

Table 110.4 List of Procedures.

	Run-in (14-17 days)	Double-blind Treatment (+ 3 days of specified date) in weeks					
Week	-2	0	1	2	3	6	12
Visit [a]	1	2	3	4	5	6	7[b]
Baseline Information							
Medical History and Ongoing medications	X						
12-lead ECG/Pregnancy test (if needed)//consent	X						
Efficacy							
Walking test	X	X				X	X
Signs/symptoms of CHF	X	X				X	X
Dyspnea –fatigue index		X					X
Echocardiography	X	X					X
Quality of life		X					X
Safety							
Vital Signs	X	X	X	X	X	X	X
Routine laboratory			X	X			X
Adverse events		X	X	X	X	X	X
Other							
Concomitant medications		X	X	X	X	X	X
Dispense medications	X	X	X	X	X	X	
Drug accountability		X	X	X	X	X	X

a. Visit 1 took place at the beginning of the run-in visit; visit 2-7 occurred at the end of the relevant weeks.

b. For subjects withdrawn after randomization. This was their final visit. Only creatinine, BUN, K+, Na+, and Cl-was

measured.
c. Echocardiography was performed at baseline to demonstrate a left ventricular EF < 45%.
d. A standard echocardiograph was sent to the central laboratory.

Dosing:

During the open-label period, subjects were left on their stable dose of ACE-inhibitor. After randomization subjects were started on randomized treatments either valsartan 80- mg daily or enalapril 5-mg BID. The medication was administered in a double-dummy format. After one week, assuming that the subject sustained no hypotension and/or no increase in creatinine values (> 50% above baseline), the dose of valsartan was increased to 160 mg daily and the enalapril dose increased to 10 mg BID.

[Comment: The maximum labeled dose for CHF for enalapril is 40 mg daily. The dose used here was only 20 mg/day.]

Consequence of amendments:

1. Subjects are to take their stable ACE medication on morning of the day of randomization
2. The criteria for time since PTCA was increased to 6 months. Subjects with persistent symptoms of hypotension (presumable after treatment with either enalapril of valsartan)1 were excluded. The upper reference range for laboratory safety was included
3. If the subject was hypotensive at the attempt to increase dose of either valsartan or enalapril, the patient was dropped from the study. If, however, the patient initially tolerated the dose increase but subsequently developed symptoms of hypotension, the dose increase could be retried up to visit 6. Subjects that do not tolerate up-titration following an adverse event, the subject is to remain on the lower dose.

Oversight:

The protocol and report do not define any standing committees with oversight responsibilities. In the statistical submission refers to a RAP meeting on March 20, 2000, which reviewed the dropouts.

Results:

A total of approximately 200 subjects from 15 sites were to be enrolled with the anticipation of 130 subjects completing. In actuality 146 patients from13 sites were enrolled and 141 subjects were randomized. The disposition of patients during the study is shown in Table 110.5

Table 110.5 Patient Disposition.

	Total Enrolled =146 D/C during run-in = 5 Randomized = 141	
	Valsartan	Enalapril
Enrolled	70	71
Completed	65	62
Discontinued	5	9
Died	1	5
Adverse Event	2	3
Withdrew consent	2	1

More subjects discontinued from the enalapril than the valsartan group. There were 5 enalapril patients who died and 1 valsartan patient who died.

Baseline demographics:

The baseline demographics are shown in Table 110.6

Table 110.6 Demographic among those enrolled in study 110.

	Valsartan (n=70	Enalapril (n=71)
Age mean + SD	68.0 ± 8.7	67.2 ± 9.4
Age > 65 (%)	44 (63%)	6 (65%)
Gender Male (% male)	49 (70%)	56 (79%)
Race (%Caucasian)	70 (100%)	71 (100%)
Weight Mean ± SD	82.8 ± 15.5	81.0 ± 16.6
NYHA Class II/III n (%)	50 (71%)/ 20(29%)	50 (70%) / 21 (30%)
Etiology of CHF		
Ischemic	47 (67%)	39 (55%)
Non-ischemic	23 (33%)	32 (45%)
Idiopathic cardiomyopathy	18 (26%)	26 (37%)
Hypertension	3 (4%)	1 (1%)
Other	2 (3%)	5 (7%)
Clinical signs n (%)		
Paroxysmal nocturnal dyspnea	1 (1%)	4 (6%)
Dyspnea at rest	1 (1%)	0
dyspnea on effort	69 (99%)	71 (100%)
Fatigue	65 (93%)	64 (90%)
Orthopnea	5 (7%)	5 (7%)
Jugular venous distension	8 (11%)	6 (9%)
Edema	8 (11%)	10 (14%)
Rales	2 (3%)	5 (7%)
Third heart sound	5 (7 %)	6 (9%)

The groups are well balanced with respect to most demographic characteristics. With respect to CHF etiology, most subjects' CHF was due to ischemic causes. Among the non-ischemic causes the most common etiology was idiopathic cardiomyopathy. Only dyspnea on effort and fatigue were frequently reported symptoms among those enrolled.

Concomitant mediations at baseline:

ACE-inhibitors and dose used during open-labeled period. There was a large degree of variation in the use of ACE-inhibitors during the open-labeled period. The median dose of the ACE-inhibitor was, in general less than the maximal dose for the treatment of heart failure. Some of these ACE inhibitors have no CHF indication.

Table 110.7 ACE-inhibitors used during the period prior to randomization

		Captopril	Cilazapril	Enalapril	Lisinopril	Quinapril	Ramipril
Enalapril	# Subjects	17		20	5	1	28
	mean dose	107		17.5	14.0	20	8.3
	min -max	50-150		5-40	10-20	20-20	0.6-10
Valsartan	# Subjects	13	1	26	5		24
	mean dose	86	5.0	17	20.0		8.4
	min -max	2.5-150	5.0-5.0	10-20	20-20		2.5-10

Concomitant medications are shown in Table 110.8. Between 76-84% of those enrolled were on loop diuretics. Beta-blockers were used in 65-70% of hose enrolled. Cardiac glycosides were used in 37-49% of those enrolled. More valsartan than enalapril subjects patients were on HMGCOA reductase inhibitors (53 versus 37%).

Table 110. 8 Concomitant medications at baseline (> 5 subjects in any treatment) N (%)

Type of Medication	Enalapril (N= 71)	Valsartan (N=70 %)
Biguanides		

Metformin	2 (3%)	6 (9%)
Vitamin K antagonists Warfarin or Warfarin sodium	 26 (37%)	 32 (36%)
Sulfonyureas Glibenclamide Glipizide	 4 (6%)	 5 (75) 1 (1%)
Platelet Aggregation inhibitors Acetylsalicylic Acid Dipyridamole	 31 (44%) 1 (1%)	 35 (50%)
Cardiac Glycosides Digitoxin Digoxin	 1 (15) 31 (44%)	 1 (1%) 25 (36%)
Organic Nitrates Nitroglycerin Isosorbide dinitrate Isosorbide mononitrate	 18 (25%) 2 (3%) 10 (14%)	 21 (30%) 2 (3%) 10 (14%)
Loop Diuretics Bumetanide Furosemide Torsemide	 1 (1%) 53 (75%)	 59 (84%) 3 (4%)
Aldosterone antagonists Spironolactone	 9 (13%)	 4 (6%)
Beta blockers Betaxolol Bisoprolol Metoprolol Carvedolol	 8(11%) 26 (37%) 12 (17%)	 1 (1%) 3 (4%) 30 (43%) 14 (20%)
HMG COA Reductase Inhibitors Fluvistatin Pravastatin Simvastatin	4 (6%) 3 (4%) 19 (27%)	3 (4%) 1(1%) 8 (9%) 27 (39%)
Preparations Inhibiting Uric Acid Production Allopurinol	 13 (18%)	12 (17%)
Benzodiazapine related drugs Zolpidem Zopiclone	 4 (6%)	 5 (7%) 6 (9%)

Six minute walk distance:
The prespecified analysis is unclear. The initial protocol did not pre-specify how dropouts due to death or worsening CHF were to be handled. The statistical report dated 20 December 2000 after all subjects completed the study defines how values for these dropouts would be imputed. Below are the two estimates of the six-minute walk. One estimate treats those who died as a last observation carried forward and the second analysis treats those who died or discontinued due to worsening heart failure by imputing a "0" value for last metric.

The timing of the measurement relative to dosing is not stated.

Table 110.9. Six-minute walk, Patients who died or were unable to exercise due to CHF were not assigned a value of "0".

Week	Treatment	N	Baseline Mean	LS mean change (SE)	Treatment difference
Week 6	Valsartan	64	417	-2.56 ± 5.7	-1.73 ± 7.7
	Enalapril	66	428	-0.83 ± 5.6	
Week 12	Valsartan	65	417	3.4 ± 6.0	-9.3 ± 8.3
	Enalapril	66	432	12.7 ± 6.0	
Endpoint	Valsartan	67	422	1.4 ± 5.9	-10.0 ± 8.0
	Enalapril	67	426	11.5 ± 5.9	

Table 110.10 contains the sponsor's analysis of the change from baseline in 6-minute walk. This analysis imputes a value of 0 for those who discontinue due to death or worsening heart failure.

Table 110.10 Patients who died or were discontinued due to death or were unable to walk due to worsening heart were assigned a value of 0.

Week	Treatment	N	Baseline Mean	LS mean change (SE)	Treatment difference
Week 6	Valsartan	64	417	-2.56 ± 5.7	-1.73 ± 7.7
	Enalapril	66	428	-0.83 ± 5.6	
Week 12	Valsartan	65	417	5.1 ± 8.8	3.4 ± 11.9
	Enalapril	66	429	2.2 ± 8.6	
Endpoint	Valsartan	67	422	3.0 ± 8.5	1.1 ± 11.6
	Enalapril	67	426	1.9 ± 8.5	

In neither analysis was valsartan superior to enalapril. Numerically, applying a last observation carried forth analysis enalapril increases six-minute walk by approximately 10 meters over valsartan. Applying a worse outcome to those, which died or could not exercise due to worsening CHF, valsartan increased walking distance by approximately 1 meter.

Secondary end points
Dyspnea-fatigue index:

The dyspnea fatigue index values are shown below. The higher the value the better the performance. There were essentially no differences between treatments.

Table 110.11 Dyspnea-fatigue index study 110.

	N=	Mean baseline value	LSM change ± SR
Valsartan	67	6.85	0.24 ± 0.16
Enalapril	64	6.73	0.26 ± 0.16

Minnesota living with heart failure questionnaire

This metric was listed as the overall score (there were 21 components to the questionnaire, one was excluded since the majority of patients did not answer this question). The maximum value for each question was 5 (worst outcome) and the minimum value was "0". The maximum worse score is therefor 100, the maximum best score was 0. At baseline, the population was only modestly compromised with their CHF. There was a trend for the enalapril group to have fewer symptoms at baseline. There was modest worsening of the score at end of study for both groups.

Table 110.12 Minnesota living with heart failure questionnaire data.

	Enalapril			Valsartan		
	Baseline	Endpoint	Change	Baseline	Endpoint	Change
N	64	64	64	67	67	67
Mean ± SD	18.2 ± 13	19.4 ± 14.6	1.2 ± 9.9	21.0± 16	21.8 ± 16.1	0.71± 11.2
Median	15.4	16.5	1.6	17	20	0.0
(min to max)	0 to 57	0 to 56	-28 to 26	1 to 67	(0 to 78)	(-28 to 30)
95% confidence interval treatment difference (-3.78, 3.35)						

The Minnesota living with heart failure questionnaire is divided into several dimensions (physical, emotional, and economic). The sponsor only analyzed the physical and emotional dimension. There were no differences between enalapril and valsartan (data not shown).

Atrio-ventricular plane displacement:

The results of the atrio-ventricular plane changes are shown in Table 110.13. An increase in excursion implies benefit. There was no difference between treatments. **[Comment: It should be noted that both treatments are afterload reducers and contraction, therefore was to some extent dependent on the degree of BP drop at the time of measurement.]**

Table 110.13 Atrio-ventricular plane displacement.

	Enalapril			Valsartan		
	Baseline	Endpoint	Change	Baseline	Endpoint	Change
N	64	64	64	67	67	67
Mean ± SD	8.8 ± 2.2	9.1 ± 2.3	0.31 ± 1.4	8.7± 2.3	9.0 ± 2.1	0.33 ± 1.2
Median	8.6	8.8	0.25	8.4	8.9	0.2
(min to max)	4.3 to 16.2	5.5 to 17.9	-3.5 to 3.6	3.0 to 13.2	(4.3 to 13.6)	(-1.8 to 4.3)
95% confidence interval treatment difference (-0.42, + 0.46)						

Left ventricular end-diastolic diameter:

The results of the left ventricular end-diastolic diameter are shown Table 110.14. There was no difference between treatments.

Table 110.14 Left ventricular end-diastolic diameter.

	Enalapril			Valsartan		
	Baseline	Endpoint	Change	Baseline	Endpoint	Change
N	63	63	63	67	67	67
Mean ± SD	37 ± 12	34 ± 10	-2.6 ± 11	36 ± 12	32 ± 7	-3.6 ± 13
Median	33.0	32	-1.0	32	31	-1.0
(min to max)	21 to 70	22 to 75	-33 to 33	23 to 83	(24 to 67.5)	(-44 to 33.5)
95% confidence interval treatment difference (-4.90, 0.42)						

Other metrics:

NYHA Class. There was little shift in NYHA classification over time.

Table 110.15 NYHA Classification over time

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Class I	0	0	1 (2%)	2 (3%)	2 (3%)
	Class II	50 (75%)	48 (72%)	48 (72%)	47 (73%)	48 (72%)
	Class III	17 (25%)	19 (28%)	18 (27%)	15 (23%)	17 (25%)
valsartan	N	67	67	67	65	67
	Class I	0	0	1 (2%)	3 (5%)	3 (5%)
	Class II	49 (73%)	49 (73%)	48 (74%)	47 (72%)	48 (72%)
	Class III	18 (27%)	18 (27%)	16 (25%)	15 (23%)	16 (24%)

Jugular venous distension: Few patients had jugular venous distension at baseline. There were more patients who improved on valsartan relative to enalapril (5 versus 1).

Table 110.16 Jugular venous distension over time.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	60 (90%)	61 (91%)	63 (94%)	59 (92%)	62 (93%)
	Present	7 (10%)	6 (9%)	4 (6%)	5 (8%)	5 (8%)
valsartan	N	67	67	65	65	67
	Absent	65 (97%)	61 (91%)	60 (92%)	64 (99%)	66(99%)
	Present	2 (3%)	6 (9%)	5 (8%)	1 (2%)	1 (2%)

Edema: The effect of treatment on edema is shown in Table 110.17. At end of study, there were more enalapril than valsartan patients that had no edema (94 versus 87%).

Table 110.17 Edema over study.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	56 (84%)	57 (85%)	58 (84%)	61 (95%)	63 (94%)
	Trace	7 (11%)	5 (8%)	7 (11%)	3 (5%)	4 (6%)
	Feet and ankles	3 (5%)	5 (8%)	2 (3%)	0	0
	Lower legs or thighs	1 (2%)	0	0	0	0
Valsartan	N	67	67	65	65	67
	Absent	57 (85%)	59 (88%)	56 (86%)	56 (86%)	58 (87%)
	Trace	8 (12%)	7 (2%)	6 (9%)	6 (9%)	6 (9%)
	Feet and ankles	2 (3%)	0	2 (3%)	3 (5%)	3 (5%)
	Lower legs or thighs	0	0	1 (2%)	0	0

Rales: There were no differences in the distribution of rales at the end of the study.

Table 110.18. Rales during the study.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	62 (93%)	62 (93%)	64 (96%)	61 (95%)	64 (96%)
	Basilar only	4 (6%)	5 (8%)	3 (5%)	3 (5%)	3 (6%)
	> 1/3 lung fields	1 (2%)	0	0	0	1 (2%)
Valsartan	N	67	67	65	65	67
	Absent	65 (97%)	66 (99%)	64 (99%)	63 (97%)	65 (97%)
	Basilar only	2 (3%)	1 (2%)	1 (2%)	2 (3%)	2 (3%)
	> 1/3 lung fields	0	0	0	0	0

Third heart sound: More enalapril than valsartan subjects had third heart sounds at baseline. There appeared to be no difference between treatments in altering third heart sounds.

Table 110.19 Third heart sound during the study.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	58 (87%)	61 (91%)	61 (91%)	60 (94%)	62 (93%)
	Present	9 (13%)	6 (9%)	6 (9%)	4 (6%)	5 (8%)
Valsartan	N	67	67	65	65	67
	Absent	64 (96%)	63 (94%)	63 (97%)	64 (99%)	66 (99%)
	Present	3 (5%)	4 (6%)	2 (3%)	1 (2%)	1 (2%)

Paroxysmal nocturnal dyspnea: More enalapril than valsartan had paroxysmal nocturnal dyspnea at baseline. There is no strong signal of benefit.

Table 110.20 Paroxysmal nocturnal dyspnea during the study.

		Week –2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	59 (88%)	67 (94%)	64 (96%)	62 (97%)	65 (97%)
	Present	8 (12%)	4 (6%)	3 (5%)	2 (3%)	2 (3%)
Valsartan	N	67	67	65	65	67
	Absent	64 (96%)	67 (99%)	65 (100%)	65 (100%)	67 (100%)
	Present	3 (5%)	1 (2%)	0	0	0

Dyspnea at rest: There were too few patients with dyspnea at rest to make any conclusion.

Table 110.21 Dyspnea at rest during the study.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	67 (100%)	67 (100%)	66 (99%)	64 (100%)	67 (100%)
	Present	0	0	1 (2%)	0	0
Valsartan	N	67	67	65	65	67
	Absent	67 (100%)	66 (99%)	65 (100%)	65 (100%)	67 (100%)
	Present	0	1 (2%)	0	0	0

Dyspnea on effort: Dyspnea upon effort was common at baseline. There was a general improvement in the enalapril group particularly among those with severe intensity at baseline. There was little change among those treated with valsartan.

Table 110.22 Dyspnea on effort during the study.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	0	0	4(6%)	2 (3%)	2 (3%)
	Slight	25 (37%)	23 (34%)	24 (36%)	30 (47%)	30 (45%)
	Moderate	30 (45%)	34 (51%)	33 (49%)	30 (47%)	32 (48%)
	Severe	12 (18%)	10 (15%)	5 (8%)	2 (3%)	3(5%)
	Very severe	0	0	1 (2%)	0	0
valsartan	N	67	67	67	65	67
	Absent	0	1 (2%)	3 (5%)	3 (5%)	3 (5%)
	Slight	24 (35%)	24 (36%)	24 (37%)	27 (42%)	28 (42%)
	Moderate	33 (49%)	35 (52%)	29 (45%)	26 (40%)	26 (39%)
	Severe	9 (13%)	6 (9%)	7 (11%)	9 (14%)	9 (14%)
	Very severe	1 (2%)	1(2%)	2 (3%)	0	1 (2%)

Fatigue: In comparing the two treatments, there is little difference in fatigue.

Table 110.23 Fatigue during the study.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	11 (16%)	7 (10%)	12 (18%)	9 (14%)	9 (13%)
	Slight	27 (40%)	27 (40%)	21 (31%)	24 (38%)	24 (36%)
	Moderate	22 (33%)	26 (39%)	28 (42%)	26 (41%)	28 (42%)
	Severe	7(1%)	7 (10%)	4 (6%)	5 (8%)	6 (9%)
	Very severe	0	0	2 (3%)	0	0
Valsartan	N	67	67	65	65	67
	Absent	7 (10%)	5 (8%)	5 (8%)	8 (12%)	8 (12%)
	Slight	33 (49%)	29 (43%)	29 (45%)	27 (42%)	28 (42%)
	Moderate	18 (27%)	26 (39%)	25 (39%)	24 (37%)	24 (36%)
	Severe	9 (13%)	6 (9%)	5 (8%)	6 (9%)	6 (9%)
	Very severe	0	1(2%)	1 (2%)	0	1 (2%)

Orthopnea: Most patients did not have orthopnea at baseline. There was no difference in treatment.

Table 110.24 Orthopnea during the study.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	63 (94%)	62 (93%)	64 (96%)	63 (98%)	66 (99%)
	Lying	3 (5%)	4 (6%)	1 (2%)	1 (2%)	1 (2%)
	0° -4 5°	1 (2%)	1 (2%)	1 (2%)	0	0
	45°- 90°	0	0	1 (2%)	0	0
Valsartan	N	67	67	65	65	67
	Absent	63 (94%)	62 (93%)	62 (95%)	64 (99%)	66 (99%)
	Lying	3 (5%)	4 (6%)	2 (3%)	1 (2%)	1 (2%)
	0° -4 5°	1 (2%)	1 (2%)	1 (2%)	0	0
	45°- 90°	0	0	0	0	0

Safety:

Duration of exposure: There were 71 patients randomized to enalapril and 70 subjects randomized to valsartan. The mean duration of exposure was 78.3 and 78.8 days respectively. The number of patient years were 15.2 and 15.1, respectively.

Dropouts/discontinuations: There were a total of 14 patients who discontinued prematurely (see table 110.5). Of these, there were 6 deaths (5 enalapril, 1 valsartan), five adverse events (3 enalapril and 2 valsartan) and 3 patients who withdrew consent (1 enalapril and 2 valsartan).

Deaths: There were a total of 6 deaths during the study one in the valsartan and five in the enalapril group. The one valsartan subject who died apparently had worsening status prior to death. Four enalapril subjects had sudden death and one died post-myocardial infarction. Capsular summaries follow:

(Valsartan): Patient # 002/008/116 was a 68 year old Caucasian male NYHA class II who had a history of diabetes mellitus (15 years) and two previous myocardial infarctions, s/p operation for mitral valve prolapse and A-V pacemaker insertion. The patient had deterioration in cardiac function on day 9 and sudden death on day 40.

(Enalapril): Patient # 006/004/203 was a 66 year old Caucasian male (NYHA class III) with a history of MI and hyperlipidemia. On day 57 of the study the patient vomited without other symptoms. The patient was found dead the next morning.

(Enalapril): Patient # 006/011/238 was a 53 year old Caucasian male (NYHA class II) with a history of dilated cardiomyopathy. On day 43 the patient was found dead.

(Enalapril) Patient # 006/015/178 was a 69 year old Caucasian male NYHA Class II with a history of diabetes mellitus, gout and chronic bronchitis. The patient died suddenly on day 51.

(Enalapril) Patient # 007/021/122 was a 68 year old Caucasian male NYHA class II with a history of hypertension died suddenly on day 21. On autopsy the patient had central organ congestion and a dilated left ventricle.

(Enalapril) Patient # 011/003/159 was a 78 year old Caucasian male NYHA Class III with a history of MI and angina. On day 64 the subjects was hospitalized with suspected myocardial infarction (CK-MB =13 ug/l and troponin I =26 ug/l) exacerbation of heart failure and bacterial infection. At the time the patient was hospitalized, the patient had an increase in serum creatinine. The patient died 4 days after admission.

Serious adverse events: There were a total of five valsartan patients and six enalapril patients who had non-lethal serious adverse events. Capsular summaries follow. Those who withdrew are noted.

(Valsartan) Patient # 001/014/244 was an 82-year old Caucasian female NYHA Class II. On day 82 she was hospitalized for worsening heart failure. Her dose of furosemide was increased and she was discharged three days later.

(Valsartan) Patient 002/01/194 was a 75-year old Caucasian male NYHA class II was hospitalized for vertigo, eventually diagnosed as benign positional vertigo.

(Valsartan) Patient 002/021/213 was a 76-year old Caucasian female NYHA III had a syncopal episode. She was hospitalized for three days and treated with furosemide.

(Valsartan) patient # 007/001/133. This was a 75-year old Caucasian female NYHA class III with a history of angina (infrequent). She was hospitalized on day 38 for unstable angina pectoris, treated with low molecular weight heparin and intravenous furosemide. Subsequent to the event, the subject's six-minute walk deteriorated and her X-ray consistent with worsening of CHF status.

(Valsartan, withdrew) Patient 013/002/173 was a 53-year old Caucasian male NYHA class III and a previous history of MI. On day 2 of therapy the patient was hospitalized for worsening of heart failure. The patient withdrew from the study.

(Enalapril) Patient # 001/009/108 was a 79-year old Caucasian male NYHA class II. The patient was hospitalized on day 15 due to chest pain. There was no evidence of myocardial infarction. There was however evidence of worsening angina. The patient had worsening in heart failure. The patient recovered and was discharged after two days.

(Enalapril, withdrew) Patient # 001/011/241 was a 68 year old Caucasian male NYHA class II with a history of MI and ischemic heart disease. This patient was hospitalized on day 75 for severe chest pain. CK-MB and troponin T values confirmed the diagnosis of myocardial infarction. The patient was treated with angioplasty and stenting and was withdrawn from the study.

(Enalapril, withdrew) Patient 001/013/243 was an 82-year old Caucasian female NYHA class III with a history of cranial arteritis. She was hospitalized on day 12 with a urinary tract infection. Serum concentration at the time of the event was > 200 umol /L. The study drug was discontinued. The patient recovered three days later.

(Enalapril, withdrew). Patient 002/012/195 was a 75-year old Caucasian female NYHA class II with a history of idiopathic cardiomyopathy. On day 57 the patient developed renal impairment (serum creatinine 491 umol/l) as well as tiredness. Ten days after discontinuation the creatinine decreased to 200 umol/l (baseline creatinine was 132 umol/L) and the tiredness resolved.

(Enalapril) Patient # 001/006/152 was an 80-year old Caucasian male NYHA Class III. This patient had a history of asthma. On day 38 the subject had symptoms that included edema of the lips and tongue. The patient was treated with intravenous adrenaline, hydrocortisone and clemastine. The reaction abated several hours later. The study drug was originally stopped but subsequently restarted. The attribution of the event was to ketoprofien. **[Comment: Gutsy or stupid to attribute this event to other than study drug (ACE-inhibitor or AII blocker)].**

(Enalapril) Patient # 011/012/191 was a 68 year old Caucasian female NYHA class III. The patient was hospitalized on day 32 of the study due to a viral syndrome. The patient also had worsening of CHF and was hospitalized again 8 days later, treated with spironolactone and discharged after one day.

Patients who withdrew due to non serious adverse events:

(Valsartan, withdrew) patient # 002/018/211 was a 65 year old Caucasian male NYHA Class II. The patient had dizziness on day 1 and was withdrawn 7 days later.

(Valsartan, withdrew) patient # 004/007/120 was a 90 year old Caucasian male NYHA class III was withdrawn from the study after 36 days because of pneumonia.

(Enalapril, withdrew) Patient # 006/006/205 was a 72year old Caucasian male NYHA class II who withdrew due to nausea and vomiting.

Patients who had dose reductions:

Those who had their doses reduced and the reason for the reduction are shown below:

Table 110.25 Patients who had dose reductions.

Patient #	Tx	Demographics	Reason
007/002/134	Val	62y/o Caucasian female	Headache and palpitations
007/006/138	ENA	73 y/o Caucasian male	Dizziness
008/007/251	ENA	56 y/o Caucasian male	vertigo
011/014/225	ENA	65 y/o Caucasian male	Bronchitis
012/010/171	ENA	81 y/o Caucasian male	Vertigo

Events classified as "severe" intensity. There were a total of 8 events (not necessarily 8 subjects) whose intensity of the event was classified as "severe". Seven of these events were in the enalapril group and 1 in the valsartan group. The events are tabulated in Table 110.26

Table 110.26 patients who had events categorized as "severe" in intensity.

Event	Enalapril	Valsartan
Myocardial infarction	2	
Ventricular Fibrillation	1	
Sudden Death	2	
Hypersensitivity	1	
Pneumonia	1	1

Overall adverse events:
Adverse events that occurred in 2 patients in either group are listed below:

Table 110.27 Overall adverse events which occurred in > 2 subjects in either group.

Event	Enalapril (n=71)	Valsartan (n=70)
Any Adverse event	45 (63%)	35 (50%)
Cardiac failure aggravated	1 (1%0	4 (6%)
Headache	1 (1%)	4 (6%)
Dizziness excluding vertigo	6 995)	3 (45)
Diarrhea	2 (3%)	3 (4%)
Nasopharyngitis	6 (9%)	2 (3%)
Back pain	4 (6%)	1 (1%)

Chemistry laboratory values (group mean):
Blood for laboratory tests were drawn on baseline and at the end of study. In addition creatinine, BUN, potassium, sodium, chloride and bicarbonate were measured at visit 3 and 4. The group mean-change from baseline to week 12 is shown below.

Table 110.28. Baseline and change from baseline to final laboratory measurement

	Enalapril			Valsartan		
Parameter	N=	Baseline	Change	N=	Baseline	Change
SGPT (UKAT/L)	63	0.5 ± 0.4	0.03 ± 0.4	62	0.5 ± 0.2	0.03 ± 0.2
SGPT (UKAT/L)	62	0.5 ± 0.2	-0.03 ± 0.1	60	0.4 ± 0.1	0.01 ± 0.1
Creatinine (Umol/L)	63	100 ± 25	3.7 ± 26	62	102 ± 26	2.9 ± 14
Albumin (Umol/L)	60	39 ± 3.4	0.6 ± 2.3	61	36 ± 3.2	-0.3 ± 2.5
Uric Acid (Umol/L)	56	417 ± 109	4.5 ± 58	60	445 ± 88	13.2 ± 61
Sodium (Mmol/L)	64	140 ± 2	-0.1 ± 2.3	64	139 ± 3	0.6 ± 2.8
Potassium (Mmol/L)	63	4.2 ± 0.3	0.07 ± 0.3	60	4.2 ± 0.3	-0.08 ± 0.3
Chloride (Mmol/L)	51	104 ± 4	-0.3 ± 4	54	103 ± 4	-0.1 ± 4
Bicarbonate (Mmol/L)	46	26 ± 3	-0.3 ± 2	47	26.3 ± 3	-0.1 ± 2
Urea (mmol/L)	58	7.7 ± 2	0.4 ± 2	63	8.4 ± 3	0.1 ± 1
Cholesterol (mmol/L0	59	5.4 ± 1	0.02 ± 0.6	63	5.7 ± 1.4	-0.4 ± 1

Chemistry values extreme: The number of subjects who exceeded the extremes in lab values is shown below. Of note, that exceeding the extreme particularly if the baseline measurement is low may not arise to a level of concern.

Table 110.29 Number of subjects and criteria for extremes .

		Decrease		Increase	
		Criteria		Criteria	
SGOT	Valsartan	None	0	>150%	0
	Enalapril		0		2
SGPT	Valsartan	None	0	>150%	0
	Enalapril		0		0
Creatinine	Valsartan	None	0	>50%	1
	Enalapril		0		1
Uric acid	Valsartan	None	0	> 50%	1
	Enalapril		0		0
Sodium	Valsartan	5%	0	>7%	0

	Enalapril		0		0
Potassium	Valsartan	20%	0	> 20%	1
	Enalapril		0		3
BUN	Valsartan	None	0	>50%	1
	Enalapril		0		2
Creatinine	Valsartan	None	0	>50%	2
	Enalapril		0		1
Sodium	Valsartan	>5%	1	>7%	0
	Enalapril		1		0
Potassium	Valsartan	20%	0	>20%	2
	Enalapril		0		5
BUN	Valsartan	None	0	>50%	2
	Enalapril		0		5

Hematologic values group means:

Hematologic values to end of treatment are shown below.

Table 110.30 Baseline and change from baseline of hematologic parameters till end of treatment.

	Enalapril			Valsartan		
Parameter	N=	Baseline	Change	N=	Baseline	Change
Hemoglobin (G/L)	64	140 ± 14	0.3 ± 7	63	143 ± 14	-2.0 ± 8
Hematocrit (%)	63	42 ± 4.0	0 ± 2.0	61	43 ± 4.2	-0.8 ± 2.8
WBC (10^9)	64	7.4 ± 1.7	0.3 ± 1.8	63	7.4 ± 1.9	0.11 ± 1.2
Platelets (10^9/L)	62	212 ± 53	3.0 ± 27	60	223 ± 47	-2.6 ± 32

Extremes in hematology: Extreme values in hematology are listed in Table 110.31

Table 110.31 Hematologic values as extreme and criteria to define a value as extreme (sponsor's criteria)

		Decrease		Increase	
		Criteria		Criteria	
Hemoglobin	Valsartan	>20%	1	>50%	0
	Enalapril		0		0
Hematocrit	Valsartan	>20%	1	>50%	0
	Enalapril		0		0
WBC	Valsartan	>50%	0	>50%	1
	Enalapril		0		3

Urinalysis:

Positive urine protein increased with both treatments.

Table 110.32 Urinalysis values

Parameter	Baseline	Valsartan		Enalapril	
		# Negative (%)	# Positive (%)	# Negative (%)	# Positive (%)
Glucose	Negative	54 (92%)	1 (2%)	53 (93%)	0
	Positive	1 (2%)	3 (5%)	1 (2%)	3 (5%)
	Total	55 (93%)	4 (7%)	54 (95%)	3 (5%)
Blood	Negative	44 (76%)	5 (9%)	48 (84%)	4 (7%)
	Positive	3 (5%)	6 (10%)	3 (5%)	2 (4%)
	Total	47 (81%)	11 (19%)	51 (90%)	6 (11%)
Protein	Negative	32 (55%)	9 (16%)	28 (49%)	10 (18%)
	Positive	6 (10%)	11 (19%)	4 (7%)	15 (26%)
	Total	38 (66%)	20 (35%)	32 (56%)	25 (44%)

Adverse events that are often reflected in laboratory abnormalities:

Events related to laboratories that either are likely to be reflected in laboratory measurements or are these measurements are shown below.

Table 110.32 Adverse events consistent with laboratory abnormalities.

Valsartan		Enalapril	
Patient Number	Abnormality	Patient Number	Abnormality
002/013/196	UTI	01/013/246	UTI
002/021/213	Hypercholesterolemia	002/001/109	UTI, hematuria
005/003/125	UTI	002/014/195	Renal insufficiency, gout
005/006/130	Hematuria	0089/001/171	Gout
005/008/132	Hyperglycemia		
009/002/142	Gout		

Laboratory values this reviewer considered noteworthy:

Table 110.33 Noteworthy laboratory values

Treatment	Pt #	Parameter	Normal range*	Value (visit #)
Valsartan	001/010/107	Uric acid	120-480 umol/l	320 (V1) 546 (V7)
Valsartan	002/008/116	Creatinine	60-115umol/l	129 (V1), 163 (V3), 202 (V4)
Valsartan	002/021/216	Sodium	136-147 mmol/l	134 (V!); 127 (V3); 137 (V4)
Valsartan	004/001/117	Potassium	3.4-5.0 mmol/l	4.2 (V1); 4.3 (V3), 4,8 (V4); 5,4 (V7)
Valsartan	008/008/252	Hemoglobin	115-170 g/l	160 (V1); 125 (V7)
Valsartan	008/008/252	Hematocrit	35-48%	49 9V1); 37 (V7)
Valsartan	011/013/192	Urea	2-10 mmol/l	7.7 (V1); 7.3 (V3);10,1 (V4); 10.5 (V7)
Valsartan	011/013/192	Creatinine	60-115umol/l	87 (V1); 103 (IV3); 113 (V4); 161(v7)
Valsartan	004/001/117	Urine Protein	Negative	Neg (V1); 2+ (V7)
Valsartan	005/011/224	Urine Protein	Negative	Neg 9V1); 3+ (V7)
Enalapril	002/012/195	Urea	2-10 mmol/l	11.4 (V1); 15 (V3); 16.6 9V4); 23,1 (V7); 14 (other)
Enalapril	002/012/195	Creatinine	60-115umol/l	132 (V1); 206 (V3),; 222 (V4); 319 (V7; 169 (other) ; 491 (other)
Enalapril	002/027/216	Urea	2-10 mmol/l	5.1 (V1); 6.4 (V30; 5.8 (V4); 9.1 (V7)
Enalapril	002/009/221	Urea	2-10 mmol/l	5.4 (V1); 6.2 (V3); 8.7 (V4); 7.8 (V7)
Enalapril	005/015/234	Urea	2-10 mmol/l	4.1 (V1); 6.6 (V3); 5.2 (V4); 4.2 (V7)
Enalapril	002/027/216	**Urea**	2-10 mmol/l	5.1 (V1); 6.2 (V3); 8.7 (V4); 7.8 (V7)
Enalapril	005/009/221	Urea	2-10 mmol/l	5.4 (V10; 6.2 (V3); 8.7 (V4)'; 7.8 (V7)
Enalapril	006/007/206	WBC	3.9-10 x 10^9	5.3 (V1); 15 (V7)
Enalapril	008/006/250	SGPT	0.2-0.8 ukat/l	0.32 (V1); 3.34 (V7)
Enalapril	012/007/168	Sodium	136-147 mmol/l	137 (V1); 130 (V3); 132 (V4); 131 (V7)
Enalapril	002/001/109	Urine Blood	Negative	Trace (V1); 2+ (V7)

* There were several laboratories and a range was constructed by the extremes of laboratories.

Vital signs: Vital signs were measured at each visit. The protocol stipulates that the timing of the measurements was to be the same at each visit. The timing relative to dose is not stated.

Sitting diastolic and systolic blood pressures are shown below. Figure 110.1 and 110.2, pulse in figure 110.3 With the exception of week 12 for valsartan both diastolic and systolic blood pressures decreased. The week 2 systolic blood pressure for the valsartan group shows an excessive and unexplainable drop.

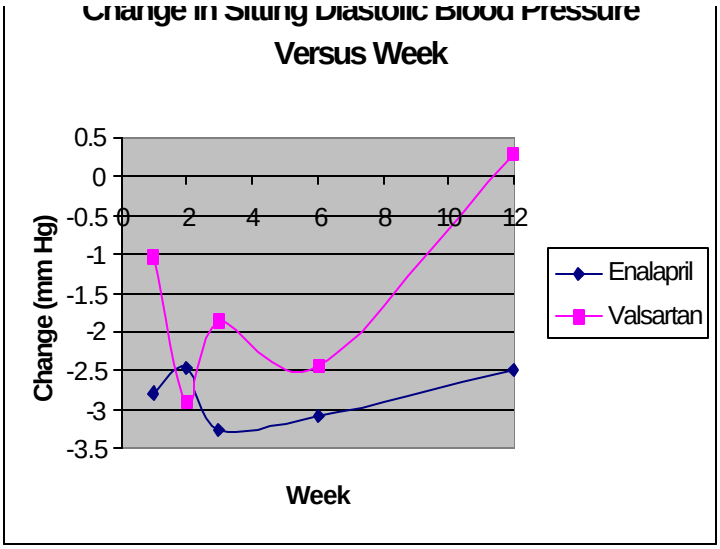


Figure 110.1 Diastolic blood pressure

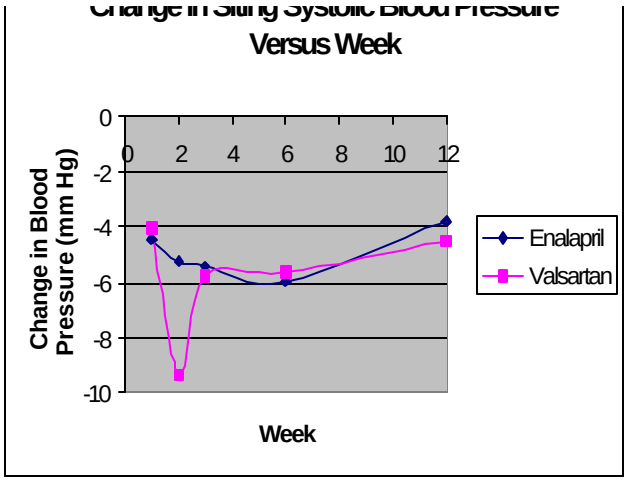
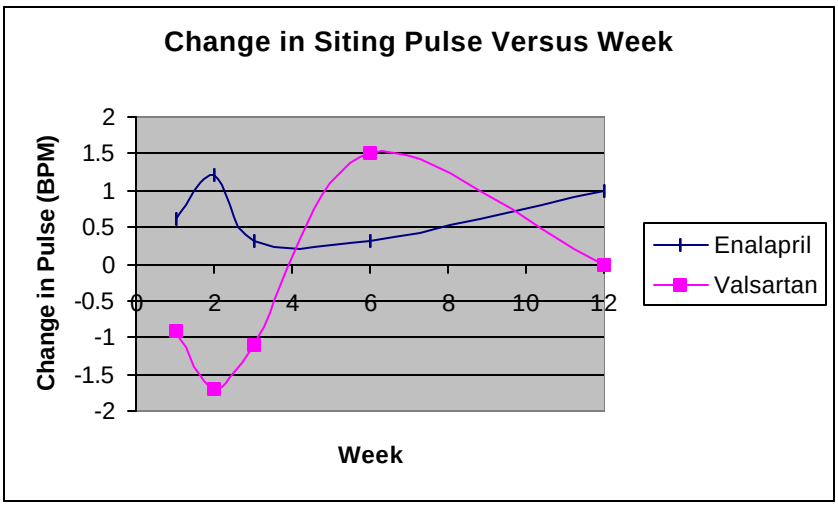


Figure 110.2 Systolic blood Pressure

With respect to pulse, there is a small increase throughout the observation period for enalapril and no consistent pattern for the valsartan.

Figure 110.3 Sitting Pulse



Orthostatic measurements: Orthostatic measurements were not taken

ECGs:

ECGs were only collected at baseline.

Discussion:

This was a decent sized study comparing enalapril at a maximum dose of 10-mg BID to Valsartan at a dose of 160-mg daily. The maximal dose of enalapril based on current labeling is, however, 40 mg/day. Subjects who entered the study were NYHA class II-III patients who were on some dose of ACE-inhibitors for at least 3 months and stable doses for > 2 weeks before entry.

Baseline ACE inhibition may not have been adequate (that is the drug may not be optimum drug and the dose may not have the optimum dose).

The primary metric of interest was six-minute walk. Baseline distance walked was approximately 420 meters. Any large increases in this metric would, therefore, be unlikely (assuming that a healthy subject could walk a mile in 20 minutes, the distance walked in six minutes would be approximately 483 meters). A reasonable maximal increase for any individual would therefore be about 60 meters.

This study should be considered a randomized withdrawal study. That is going from some dose of ACE-inhibitor to either similar or different therapy. The time course of deterioration in exercise performance after the withdrawal of ACE-inhibitors in CHF subjects is not known. Since there was no measurement of walk distance prior to the start of the ACE-inhibitor, the benefit of ACE-inhibitors on six-minute walk for those enrolled is also unknown and the consequence of their discontinuation is uncertain.

The original protocol was silent as to how to impute data for those who discontinue during the study. The first specific plan was submitted on 20 December 2000, well after all patients completed the study. This plan imputed a worst outcome for those who died or were too symptomatic to exercise. There were more of these patients treated with enalapril who died during the course of the study and imputing a worst outcome favors valsartan. The deaths of the m enalapril-treated patients were in general, sudden in nature and did not therefore reflect the deterioration in pump function. Imputing a zero value for exercise under these circumstances is not an obvious choice as to how to handle missing data. Imputing a last value carried forth is equivalently valid for the study.

If one imputes a last value carried forth for the study the enalapril group had a least square mean change of 10 meter increase in 6-minute walk when compared to valsartan. If one imputes a worse outcome for those who died or were unable walk due to worsening heart failure valsartan had a 1-meter increase in walk distance relative to enalapril. Neither analysis shows a difference between groups.

There were four secondary end points measured within the study, dyspnea fatigue index, Minnesota Living with heart failure questionnaire, atrio-ventricular plane displacement and left ventricular end diastolic diameter, none of these parameters differed between the two treatment groups.

There were in addition a total of 10 additional metrics collected (NYHA classification, jugular venous distension, edema, rales, 3rd heart sound, paroxysmal nocturnal dyspnea, dyspnea at rest, dyspnea on effort, fatigue and orthopnea), none of these were preferentially altered by either treatment.

With respect to safety, there were five deaths among those treated with enalapril and one death among those treated with valsartan. Capsular summaries do not suggest a relationship to treatment. Overall adverse events are not unusual.

Conclusion:

This study does not support a benefit of valsartan on six-minute walk.

This study does not support a claim of non-inferiority.
There were no safety issues.